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(54) Title: **MELANIN CONCENTRATING HORMONE RECEPTOR LIGANDS: SUBSTITUTED 2-(4-BENZYL-PIPERAZIN-1-YLMETHYL)- AND 2-(4-BENZYL-DIAZEPAN-1-YLMETHYL)-1H-BENZOIMIDAZOLE ANALOGUES**

(57) Abstract: Melanin concentrating hormone receptor ligands (especially substituted 2-(4-benzyl-piperazin-1-ylmethyl)-1H-benzoimidazole analogues), capable of modulating MCH receptor activity, are provided. Such ligands may be used to modulate MCH binding to MCH receptors in vivo or in vitro, and are particularly useful in the treatment of a variety of metabolic, feeding and sexual disorders in humans, domesticated companion animals and livestock animals. Pharmaceutical compositions and methods for treating such disorders are provided, as are methods for using such ligands for detecting MCH receptors (e.g., receptor localization studies).

MELANIN CONCENTRATING HORMONE RECEPTOR LIGANDS:
SUBSTITUTED 2-(4-BENZYL-PIPERAZIN-1-YLMETHYL)- AND 2-(4-BENZYL-
DIAZEPAN-1-YLMETHYL)-1H-BENZOIMIDAZOLE ANALOGUES

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FIELD OF THE INVENTION

This invention relates generally to substituted benzoimidazole analogues that are modulators of melanin concentrating hormone receptors, and to the use of such compounds for treating a variety of metabolic, eating and sexual disorders. The invention further relates to the use of such compounds as probes for the detection and localization of MCH receptors.

DESCRIPTION OF THE SEQUENCE LISTING

SEQ ID NO:1	Cynomolgus macaque MCH1R DNA sequence
SEQ ID NO:2	Cynomolgus macaque MCH1R amino acid sequence
15 SEQ ID NO:3	Forward cloning primer
SEQ ID NO:4	Reverse cloning primer

BACKGROUND OF THE INVENTION

Melanin concentrating hormone, or MCH, is a cyclic 19 amino acid neuropeptide that functions as a regulator of food intake and energy balance. MCH is produced in the hypothalamus of many vertebrate species, including humans, and serves as a neurotransmitter in the lateral and posterior hypothalamus. Both of these regions are associated with behaviors such as eating, drinking, aggression and sexual behavior. MCH is also produced at various peripheral sites, including the gastrointestinal tract and testis.

The postulated role of MCH in feeding behavior and body weight is confirmed by the finding that i.c.v. injection of MCH into the lateral ventricle of the hypothalamus increases caloric consumption in rats over similarly treated control animals. Furthermore, rats having the *ob/ob* genotype exhibit a 50-80% increase in MCH mRNA expression as compared to leaner *ob/+* genotype mice. MCH knockout mice are leaner than genetically identical, but normal MCH-producing mice due to hypophagia and an increased metabolic rate.

MCH activity is mediated via binding to specific receptors. Like other G protein-coupled receptors (*e.g.*, neuropeptide Y (NPY) and beta-adrenergic receptors), MCH receptors are membrane-spanning proteins that consist of a single contiguous amino acid chain comprising an extracellular N-terminal domain, seven membrane-spanning alpha helical domains (connected by three intracellular loop domains alternating with three extracellular loop domains), and an intracellular C-terminal domain. Signal transduction is initiated by the binding of MCH to the

receptor. This elicits conformational changes in the extracellular domains. When the receptor is functioning properly, these conformational changes propagate through the transmembrane domains and result in a coordinated change in the intracellular portions of the receptor. This precise alteration in the intracellular domains acts to trigger the associated G-protein complex to modulate intracellular signaling.

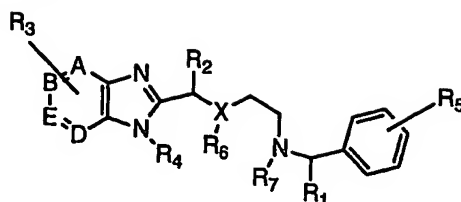
The MCH type 1 receptor (MCH1R) is a 353 amino acid, 7-transmembrane, alpha-helical, G-coupled protein receptor, first reported as orphan receptor SLC-1 Kolakowski et al. (1996) *FEBS Lett.* 398:253-58 and Lakaye et al. (1998) *Biochim. Biophys. Acta* 1401:216-220. Chambers et al. (1999) *Nature* 400:261-65 and Saito et al. (1999) *Nature* 400:265-69 then showed SLC-1 to be an MCH receptor. Immunohistochemistry studies of rat brain sections indicate that the MCH1R is widely expressed in brain. MCH1R expression is found in olfactory tubercle, cerebral cortex, substantia nigra, basal forebrain CA1, CA2, and CA3 field of the hippocampus, amygdala, and in nuclei of the hypothalamus, thalamus, midbrain and hindbrain. Strong signals are observed in the ventromedial and dorsomedial nuclei of the hypothalamus, two areas of the brain involved in feeding behavior. Upon binding MCH, MCH1R expressed in HEK 293 cells mediate a dose-dependent release of intracellular calcium. Cells expressing MCH1R also exhibit a pertussis toxin sensitive dose-dependent inhibition of forskolin-elevated cyclic AMP, indicating that the receptor couples to a $G_{i/o}$ G-protein alpha subunit.

Recently, a second MCH receptor (MCH2R) was identified (WO 01/70975; WO 01/07606; WO 00/49046; An et al., *Proc. Natl. Acad. Sci. USA* (2001) 98:7576-7581; Sailer et al., *Proc. Natl. Acad. Sci. USA* (2001) 98:7564-7569; Hill et al., *J. Biol. Chem.* (2001) 276:20125-20129; Mori et al., *Biochem. Biophys. Res. Commun.* (2001) 283:1013-1018). MCH2R has an overall amino acid identity of more than 30% with MCHR1, and is detected specifically in most regions of the brain, with an expression pattern similar to that of MCHR1.

Because MCH is an important regulator of food intake and energy balance, agents capable of modulating the activity of MCH receptors, especially MCHR1, are highly desirable for the treatment of obesity, eating disorders (e.g., bulimia and anorexia), sexual disorders (e.g., anorgasmic or psychogenic impotence) and metabolic disorders, such as diabetes. Small molecule, non-peptide antagonists of MCH receptors would be of particular value for such therapies. The present invention fulfills this need, and provides further related advantages.

SUMMARY OF THE INVENTION

The present invention provides MCH receptor modulators that inhibit or enhance MCH binding to MCH receptor. Such modulators comprise a substituted benzoimidazole analogue that exhibits a K_i of 500 nanomolar or less, 100 nanomolar or less, or 10 nanomolar or less in an MCH receptor ligand binding assay, and is characterized by the formula:



Formula I

or a pharmaceutically acceptable salt thereof, wherein:

A, B, E, D and X each independently represent CH or N, with the proviso that not more than two of A, B, E and D represent N;

- 5 R_1 is: (i) hydrogen, $-C(=O)-NH_2$, $-SO_2NH_2$ or $-COOH$; or (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkyl ether, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- or di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- or di- $(C_1-C_8$ alkyl)sulfonamido, or mono- or di- $(C_1-C_8$ alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl;

- 10 R_2 is: (i) hydrogen, halogen, hydroxy, $-C(=O)-NH_2$, $-SO_2NH_2$ or $-COOH$; or (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkyl ether, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- or di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- or di- $(C_1-C_8$ alkyl)sulfonamido or mono- or di- $(C_1-C_8$ alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl;

- 15 R_3 represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D and is independently selected from: (i) halogen, hydroxy, amino, cyano, nitro, $-C(=O)-NH_2$, $-SO_2NH_2$ and $-COOH$; and (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- and di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- and di- $(C_1-C_8$ alkyl)sulfonamido, and mono- and di- $(C_1-C_8$ alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl;

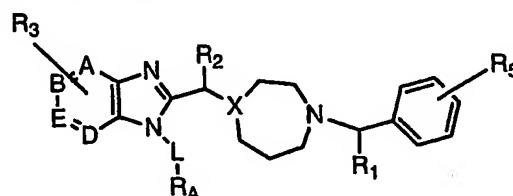
- 20 R_4 is: (i) hydrogen, $-C(=O)-NH_2$, $-SO_2NH_2$ or $-COOH$; (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- and di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- and di- $(C_1-C_8$ alkyl)sulfonamido, and mono- and di- $(C_1-C_8$ alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl; or (iii) $L-R_A$, wherein L is C_1-C_6 alkyl; and R_A is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl, halo C_1-C_8 alkyl, C_1-C_8 alkoxy, halo C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-

C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate and 5- to 10-membered carbocyclic and heterocyclic groups;

R₅ represents from 0 to 3 substituents, each of which is independently selected from: (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ and -COOH; or (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, mono- and di-(C₁-C₈alkyl)carboxamido, and fused and pendant 3- to 10-member carbocyclic and heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; and

R₆ and R₇ are each independently: (i) hydrogen, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ or -COOH; (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; or (iii) joined to form, with the XCH₂CH₂N, a 5- to 7-membered heterocyclic ring that is unsubstituted or substituted with from 1 to 3 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl.

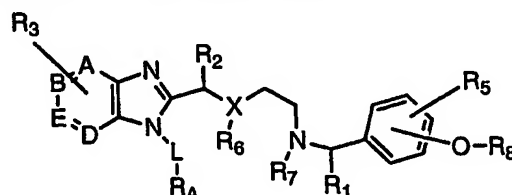
Within certain aspects, compounds provided herein have the formula:



Formula III

or a pharmaceutically acceptable salt thereof, wherein: A, B, E, D, X, R₁, R₂, R₃, R₅, L and R_A are as described above. Within certain specific embodiments L is -CH₂- or -CH(CH₃)-, and R_A is phenyl, unsubstituted or substituted with one or more substituents independently selected from hydroxy, C₁-C₈alkoxy and haloC₁-C₈alkoxy; R₁ and R₂ are independently hydrogen or C₁-C₆alkyl; and/or at least one R₅ is dioxalane, a halogen or C₁-C₄alkoxy.

Within further aspects, compounds provided herein have the formula:

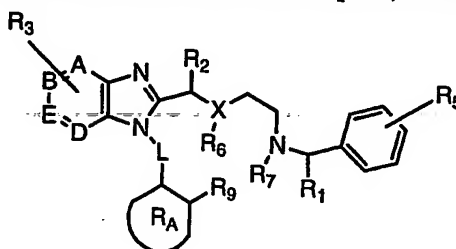


Formula IV

or a pharmaceutically acceptable salt thereof, wherein: A, B, E, D, X, R₁, R₂, R₃, R₆, R₇, L and R_A are as described above; R₅ represents from 0 to 3 substituents, each of which is independently

selected from: (i) halogen, hydroxy, amino, cyano, nitro, $-C(=O)-NH_2$, $-SO_2NH_2$, and $-COOH$; (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- and di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- and di- $(C_1-C_8$ alkyl)sulfonamido, mono- and di- $(C_1-C_8$ alkyl)carboxamido, and fused and pendant 3- to 10-member carbocyclic and heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl; and (iii) substituents that are joined to R_8 to form a 5- or 6-membered heterocyclic ring; and R_8 is hydrogen, C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_2-C_8 alkanoyl, C_2-C_8 alkyl ether, halo C_1-C_8 alkyl, halo C_1-C_8 alkoxy or a substituent that is joined to R_5 to form a 5- or 6-member heterocyclic ring.

Compounds are further provided, within other aspects, having the formula:



Formula V

or a pharmaceutically acceptable salt thereof, wherein: A, B, E, D, X, R_1 , R_2 , R_3 , R_6 , R_7 , L and R_A are as described above, and wherein R_9 is hydroxy, C_1-C_8 alkoxy, halo C_1-C_8 alkoxy, C_1-C_8 alkanoyloxy or halo C_1-C_8 alkanoyloxy.

Within further aspects, the present invention provides pharmaceutical compositions comprising a compound or modulator as described above in combination with a physiologically acceptable carrier or excipient. Within certain embodiments, a pharmaceutical composition provided herein may further comprise one or more additional active agents (*i.e.*, drugs). Pharmaceutical compositions provided herein may be formulated, for example, as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

The present invention further provides, within other aspects, methods for treating a disease or disorder associated with MCH receptor activation, comprising administering to a patient in need of such treatment an effective amount of a compound or modulator as described above. Such diseases and disorders include, for example, eating disorders (*e.g.*, obesity and bulimia nervosa), sexual disorders, diabetes, heart disease and stroke. The compound or modulator may be administered orally, or via another means such as intranasally, intravenously or topically. Within certain embodiments, the patient is a human or a companion animal.

Within further aspects, the present invention provides compounds as described above, wherein the compounds are radiolabeled.

Methods are provided, within other aspects, for determining the presence or absence of MCH receptor in a sample, comprising the steps of: (a) contacting a sample with an agent comprising a compound as described above under conditions that permit binding of the agent to MCH receptor; and (b) detecting a level of agent bound to MCH receptor. Within certain
5 embodiments, the agent is a radiolabeled compound, and the step of detection comprises the steps of: (i) separating unbound agent from bound agent; and (ii) detecting the presence or absence of bound agent in the sample. Detection may be achieved, for example, using autoradiography.

The present invention further provides, within other aspects, methods for modulating
10 binding of ligand to MCH receptor. Certain such methods are performed *in vitro*, and comprise contacting MCH receptor with a compound or modulator as described above under conditions and in an amount sufficient to detectably modulate MCH binding to MCH receptor. Other such methods may be performed *in vivo*, and comprise contacting cells expressing MCH receptor with a compound or modulator as described above in an amount sufficient to detectably modulate
15 MCH binding to cells expressing a cloned MCH receptor *in vitro*. Modulation of MCH binding may be determined, for example, using a ligand binding assay as provided herein.

Methods are further provided for modulating binding of MCH to MCH receptor in a patient, comprising administering to a patient (*i.e.*, a human or non-human animal) a compound or modulator as described above. Patients may include, for example, companion animals such as
20 dogs.

Within certain embodiments of the above methods, the modulation is inhibition and/or the MCH receptor is a human MCH receptor.

Within further aspects, the present invention provides methods for modulating the signal-transducing activity of MCH receptor, comprising contacting an MCH receptor, either *in vivo* or
25 *in vitro*, with a sufficient amount of an MCH receptor modulator, under conditions suitable for binding of MCH to MCH receptor.

Also provided by the present invention are packaged pharmaceutical preparations, comprising: (a) a pharmaceutical composition as described above in a container; and (b) instructions for using the composition to treat a patient suffering from a disease or disorder
30 associated with MCH receptor activation. Such disorders include, for example eating disorders (*e.g.*, obesity and bulimia nervosa), sexual disorders, diabetes, heart disease and stroke.

These and other aspects of the present invention will become apparent upon reference to the following detailed description.

35 DETAILED DESCRIPTION

As noted above, the present invention provides MCH receptor modulators comprising small molecule MCH receptor ligands that are substituted benzoimidazole analogues. Such

modulators may be used *in vitro* or *in vivo*, to inhibit or enhance MCH binding to MCH receptors in a variety of contexts, as discussed in further detail below.

TERMINOLOGY

5 Compounds are generally described herein using standard nomenclature. For compounds having asymmetric centers, it should be understood that (unless otherwise specified) all of the optical isomers and mixtures thereof are encompassed. In addition, compounds with carbon-carbon double bonds may occur in *Z*- and *E*- forms, with all isomeric forms of the compounds being included in the present invention unless otherwise specified. Where a
10 compound exists in various tautomeric forms, a recited compound is not limited to any one specific tautomer, but rather is intended to encompass all tautomeric forms. Certain compounds are described herein using a general formula that includes variables (*e.g.*, R_1 , n , Ar_1). Unless otherwise specified, each variable within such a formula is defined independently of other variable, and any variable that occurs more than one time in a formula is defined independently
15 at each occurrence.

 As used herein, a "2-(4-benzyl-piperazin-1-ylmethyl)- or 2-(4-benzyl-diazepan-1-ylmethyl)-1*H*-benzoimidazole analogue" or "benzoimidazole analogue" is a compound that satisfies the structure of Formula I. Such compounds include those in which R_6 and R_7 are joined to form a 6- or 7-membered ring (*i.e.*, piperazinyl or diazepanyl when X is N, or piperidinyl or hexamethyleneiminyl when X is CH). Such compounds also include those in which R_6 and R_7
20 are not so joined.

 As used herein, the term "alkyl" refers to a straight chain, branched chain or cyclic saturated aliphatic hydrocarbon. An alkyl group may be bonded to an atom within a molecule of interest via any chemically suitable portion. Alkyl groups include groups having from 1 to 8
25 carbon atoms (C_1 - C_8 alkyl), from 1 to 6 carbon atoms (C_1 - C_6 alkyl) and from 1 to 4 carbon atoms (C_1 - C_4 alkyl), such as methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, *tert*-butyl, pentyl, 2-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, 3-methylpentyl, cyclopropyl, cyclopropylmethyl, cyclopentyl, cyclopentylmethyl, cyclohexyl, cycloheptyl and norbornyl. " C_0 - C_3 alkyl" refers to a bond or a C_1 - C_3 alkyl group.

30 Similarly, "alkenyl" refers to straight or branched chain alkene groups or cycloalkene groups. Within an alkenyl group, one or more unsaturated carbon-carbon double bonds are present. Alkenyl groups include C_2 - C_8 alkenyl, C_2 - C_6 alkenyl and C_2 - C_4 alkenyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively, such as ethenyl, allyl or isopropenyl. "Alkynyl" refers to straight or branched chain alkyne groups, which have, one or
35 more unsaturated carbon-carbon bonds, at least one of which is a triple bond. Alkynyl groups include C_2 - C_8 alkynyl, C_2 - C_6 alkynyl and C_2 - C_4 alkynyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

By " C_3 - C_{10} cycloalkyl" is meant alkyl groups having 3-10 carbon atoms forming a mono-, bi-, or polycyclic ring system, such as, for example, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and norbornyl. " C_4 - C_8 cycloalkyl" and " C_5 - C_7 cycloalkyl" groups are those in which 4-8 or 5-7 carbon atoms form a single ring, respectively. Similarly, 5 " C_3 - C_{10} cycloalkenyl" refers to hydrocarbon groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system and containing one or more carbon-carbon double bonds (*e.g.*, cyclopentenyl, cyclohexenyl or cycloheptenyl). " $(C_3$ - $C_{10})$ cycloalkynyl" refers to hydrocarbon groups having 3-10 carbon atoms forming a mono-, bi, or polycyclic ring system and containing one or more carbon-carbon triple bonds.

10 The term "(cycloalkyl)alkyl" or " $(C_3$ - C_{10} cycloalkyl) C_1 - C_8 alkyl" refers to a straight or branched alkyl substituent having 1 to 8 carbon atoms, that is further substituted with a mono-, bi, or polycyclic ring system having 3-10 carbon atoms (*e.g.*, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl and cycloheptylmethyl).

The term "hydroxy C_1 - C_8 alkyl" (or "hydroxy C_1 - C_6 alkyl") refers to aliphatic groups 15 having from 1 to 8 (or 1 to 6) carbon atoms, and further comprising at least one hydroxyl group on the main carbon chain and/or on a side chain. Hydroxy C_1 - C_8 alkyl groups include, for example, 2-hydroxy-1,1-dimethyl-ethyl, 1-hydroxymethyl-2-methyl-propyl and 2-hydroxy-propyl.

By "alkoxy," as used herein, is meant an alkyl, alkenyl or alkynyl group as described 20 above attached via an oxygen bridge. Alkoxy groups include C_1 - C_8 alkoxy, C_1 - C_6 alkoxy and C_1 - C_4 alkoxy groups, which have from 1 to 8, 1 to 6 or 1 to 4 carbon atoms, respectively. Alkoxy groups include, for example, methoxy, ethoxy, propoxy, isopropoxy, n-butoxy, sec-butoxy, tert-butoxy, n-pentoxy, 2-pentoxy, 3-pentoxy, isopentoxy, neopentoxy, hexoxy, 2-hexoxy, 3-hexoxy, and 3-methylpentoxy. Similarly, " C_1 - C_8 alkylthio" refers to an alkyl group of 1 to 8 carbon atoms 25 attached via a sulfur bridge. " C_3 - C_{10} aryloxy" refers to aryl groups of 3 to 10 carbon atoms attached via an oxygen bridge (*e.g.*, phenoxy).

The term "alkanoyl" refers to an acyl group in a linear, branched or cyclic arrangement (*e.g.*, $-(C=O)$ -alkyl). Alkanoyl groups include C_2 - C_8 alkanoyl, C_2 - C_6 alkanoyl and C_2 - C_4 alkanoyl groups, which have from 2 to 8, 2 to 6 or 2 to 4 carbon atoms, respectively.

30 An "alkanone" is a ketone group in which carbon atoms are in a linear, branched or cyclic alkyl arrangement. " C_3 - C_8 alkanone," " C_3 - C_6 alkanone" and " C_3 - C_4 alkanone" refer to an alkanone having from 3 to 8, 6 or 4 carbon atoms, respectively.

Similarly, "alkyl ether" refers to a linear or branched ether substituent linked via a carbon-carbon bond. Alkyl ether groups include C_2 - C_8 alkyl ether, C_2 - C_6 alkyl ether and C_2 - 35 C_6 alkyl ether groups, which have 2 to 8, 6 or 4 carbon atoms, respectively.

The term "alkoxycarbonyl" refers to an alkoxy group linked via a carbonyl (*e.g.*, a group having the general structure $-C(=O)-O$ -alkyl). Alkoxycarbonyl groups include C_2 - C_8 , C_2 - C_6 and

C₂-C₄alkoxycarbonyl groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively. C₁alkoxycarbonyl refers to -C(=O)OH, which is encompassed by the term "C₁-C₈alkoxycarbonyl."

5 "Alkanoyloxy," as used herein, refers to an alkanoyl group linked via an oxygen bridge (e.g., a group having the general structure -O-C(=O)-alkyl). Alkanoyloxy groups include C₂-C₈, C₂-C₆ and C₂-C₄alkanoyloxy groups, which have from 2 to 8, 6 or 4 carbon atoms, respectively. C₁alkanoyloxy refers to -O-C(=O)H, which is encompassed by the term "C₁-C₈alkanoyloxy."

The term "C₁-C₈carbonate" refers to an alkoxycarbonyl group linked via an oxygen bridge. In other words, a carbonate group has the general structure -O-C(=O)-O-alkyl. C₁-C₈carbonate groups are generally preferred, with C₁-C₄carbonate groups particularly preferred.

10 The term "C₁-C₈carbamate," as used herein, refers to a group having the general structure -N-C(=O)-O-alkyl. C₁-C₈carbamate groups are generally preferred, with C₁-C₄carbamate groups particularly preferred.

The term "halogen" includes fluorine, chlorine, bromine and iodine. A "haloalkyl" is a branched, straight-chain or cyclic alkyl group, substituted with 1 or more halogen atoms (e.g., "haloC₁-C₈alkyl" groups have from 1 to 8 carbon atoms; "haloC₁-C₆alkyl" groups have from 1 to 6 carbon atoms). Examples of haloalkyl groups include, but are not limited to, mono-, di- or tri-fluoromethyl; mono-, di- or tri-chloromethyl; mono-, di-, tri-, tetra- or penta-fluoroethyl; and mono-, di-, tri-, tetra- or penta-chloroethyl. Typical haloalkyl groups are trifluoromethyl and difluoromethyl. Within certain compounds provided herein, not more than 5 or 3 haloalkyl groups are present. The term "haloalkoxy" refers to a haloalkyl group as defined above attached via an oxygen bridge. "HaloC₁-C₈alkoxy" groups have 1 to 8 carbon atoms.

A dash ("-") that is not between two letters or symbols is used to indicate a point of attachment for a substituent. For example, -CONH₂ is attached through the carbon atom.

25 A "heteroatom," as used herein, is oxygen, sulfur or nitrogen.

A "carbocycle" or "carbocyclic group" comprises at least one ring formed entirely by carbon-carbon bonds (referred to herein as a carbocyclic ring), and does not contain a heterocyclic ring. Unless otherwise specified, each carbocyclic ring within a carbocycle may be saturated, partially saturated or aromatic. A carbocycle generally has from 1 to 3 fused, pendant or spiro rings, carbocycles within certain embodiments have one ring or two fused rings. Typically, each ring contains from 3 to 8 ring members (i.e., C₃-C₈); C₅-C₇ rings are recited in certain embodiments. Carbocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Certain representative carbocycles are cycloalkyl (i.e., groups that comprise saturated and/or partially saturated rings, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, adamantyl, decahydro-naphthalenyl, octahydro-indenyl, and partially saturated variants of any of the foregoing, such as cyclohexenyl), as well as aromatic groups (i.e., groups that contain at least one aromatic carbocyclic ring, such as phenyl, benzyl,

naphthyl, phenoxy, benzoxyl, phenylethanonyl, fluorenyl, indanyl and 1,2,3,4-tetrahydronaphthyl. Carbon atoms present within a carbocyclic ring may, of course, be further bonded to zero, one or two hydrogen atoms and/or any of a variety of ring substituents, such as hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-Calkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, C₃-C₇cycloalkylC₀-C₄alkyl, haloC₁-C₈alkyl, haloC₁-C₈alkoxy, aminoC₁-C₈alkyl, hydroxyC₁-C₈alkyl, C₂-C₈alkanoyl, C₂-C₈alkoxycarbonyl, -COOH, -C(=O)NH₂, mono- or di-(C₁-C₈alkyl)carboxamido, -S(O₂)NH₂, and/or mono- or di-(C₁-C₈alkyl)sulfonamido. Within certain embodiments, C₃-C₁₀carbocycles that contain 1 carbocyclic ring or 2 fused carbocyclic rings (for a total of 3 to 10 ring members), optionally substituted, are preferred, with C₃-C₁₀carbocycles (*i.e.*, groups with from 5 to 10 ring members and optional substitution(s)) particularly preferred.

A "heterocycle" or "heterocyclic group" has from 1 to 3 fused, pendant or spiro rings, at least one of which is a heterocyclic ring (*i.e.*, one or more ring atoms is a heteroatom, with the remaining ring atoms being carbon). Typically, a heterocyclic ring comprises 1-4 heteroatoms; within certain embodiments each heterocyclic ring has 1 or 2 heteroatoms per ring. Each heterocyclic ring generally contains from 3 to 8 ring members (rings having from 5 to 7 ring members are recited in certain embodiments), and heterocycles comprising fused, pendant or spiro rings typically contain from 9 to 14 ring members. Heterocycles may be optionally substituted at nitrogen and/or carbon atoms with a variety of substituents, such as those described above for carbocycles. Unless otherwise specified, a heterocycle may be a heterocycloalkyl group (*i.e.*, each ring is saturated or partially saturated) or a heteroaryl group (*i.e.*, at least one ring within the group is aromatic). A heterocyclic group may generally be linked via any ring or substituent atom, provided that a stable compound results. N-linked heterocyclic groups are linked via a component nitrogen atom. A "heterocycleC₀-C₈alkyl" is a heterocyclic group linked via a direct bond or C₁-C₈alkyl group.

Heterocyclic groups include, for example, acridinyl, azepanyl, azocinyl, benzimidazolyl, benzimidazoliny, benzisothiazolyl, benzisoxazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzothiazolyl, benzotriazolylcarbazolyl, benzotetrazolyl, NH-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, dihydrofuro[2,3-b]tetrahydrofuran, dihydroisoquinolinyl, dihydrotetrahydrofuran, 1,4-dioxo-8-aza-spiro[4.5]dec-8-yl, dithiazinyl, furanyl, furazanyl, imidazoliny, imidazolidinyl, imidazolyl, indazolyl, indolenyl, indolinyl, indoliziny, indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isothiazolyl, isoxazolyl, isoquinolinyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, oxazolidinyl, oxazolyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, piperidinyl, piperidonyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridoimidazolyl, pyridooxazolyl, pyridothiazolyl, pyridyl, pyrimidyl,

pyrrolidinyl, pyrrolidonyl, pyrrolinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, quinuclidinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, tetrazolyl, thiadiazinyl, thiadiazolyl, thianthrenyl, thiazolyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thienyl, thiophenyl, thiomorpholinyl and variants thereof in which the sulfur atom is oxidized, triazinyl, xanthenyl
5 and any of the foregoing that are substituted with from 1 to 4 substituents as described herein.

Certain aromatic heterocycles include 5- to 10-membered heteroarylC₀-C₈alkyl groups (*i.e.*, groups in which the heterocyclic group comprising at least one aromatic ring is linked via a direct bond or a C₁-C₈alkyl group). Such groups include, for example, the heteroaryl groups recited above, as well as groups in which any of the foregoing is linked via C₁-C₈alkyl, C₁-
10 C₆alkyl or C₁-C₄alkyl. Representative aromatic heterocycles are azocinyl, pyridyl, pyrimidyl, imidazolyl, tetrazolyl and 3,4-dihydro-1H-isoquinolin-2-yl, as well as groups in which each of the foregoing is linked via C₁-C₄alkyl. Preferred heterocycloalkyls are 3- to 8-membered heterocycloalkyls such as piperidine and pyrrolidine.

A "substituent," as used herein, refers to a molecular moiety that is covalently bonded to
15 an atom within a molecule of interest. For example, a "ring substituent" may be a moiety such as a halogen, alkyl group, haloalkyl group or other group discussed herein that is covalently bonded to an atom (preferably a carbon or nitrogen atom) that is a ring member. The term "substitution" refers to replacing a hydrogen atom in a molecular structure with a substituent as described above, such that the valence on the designated atom is not exceeded, and such that a chemically
20 stable compound (*i.e.*, a compound that can be isolated, characterized, and tested for biological activity) results from the substitution. When a substituent is keto (*i.e.*, =O), then 2 hydrogens on the atom are replaced. Keto substituents are not present on aromatic moieties.

Groups that are "optionally substituted" are unsubstituted or are substituted by other than hydrogen at one or more available positions, typically 1, 2, 3, 4 or 5 positions, by one or more
25 suitable groups (which may be the same or different). Such optional substituents include, for example, hydroxy, halogen, cyano, nitro, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkyl ether, C₃-C₈alkanone, C₁-C₈alkylthio, amino, mono- or di-(C₁-C₈alkyl)amino, haloC₁-C₈alkyl, haloC₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₂-C₈alkoxycarbonyl, -COOH, -CONH₂, mono- or di-(C₁-C₈alkyl)carboxamido, -SO₂NH₂, and/or mono- or di-(C₁-
30 C₈alkyl)sulfonamido, as well as carbocyclic and heterocyclic groups. Certain optionally substituted groups are substituted with from 0 to 5 or from 0 to 3 independently selected substituents.

The term "MCH receptor" refers to a protein comprising any MCH receptor sequence (*i.e.*, a cellular protein that detectably binds MCH and mediates a dose dependent release of
35 intracellular calcium). Naturally-occurring mammalian (especially human and monkey) MCH type 1 or type 2 receptor sequences are generally preferred.

A "MCH receptor modulator," also referred to herein as a "modulator," is a compound that modulates (*i.e.*, increases or decreases) MCH binding to one or more MCH receptors, as well as MCH receptor-mediated signal transduction. In other words, a modulator may be a MCH receptor agonist or antagonist. Modulators provided herein are generally substituted 2-(4-benzyl-piperazin-1-ylmethyl)- or 2-(4-benzyl-diazepan-1-ylmethyl)-1*H*-benzoimidazole analogues. A modulator binds with "high affinity" if the K_i at an MCH receptor is less than 1 micromolar, preferably less than 100 nanomolar or 10 nanomolar. Preferred modulators bind to an MCH receptor with a K_i that is less than 500 nanomolar (more preferably less than 100 nanomolar). Assays to evaluate an effect on MCH binding to MCH receptor, as well as MCH receptor-mediated signal transduction, may be performed using the binding and calcium mobilization assays provided herein within Examples 2 and 3, respectively. A modulator is considered an antagonist if it detectably inhibits MCH binding to MCH receptor and/or MCH receptor-mediated signal transduction (using, for example, the representative assay provided in Example 3). MCH receptor antagonists include neutral antagonists and inverse agonists. A modulator binds "specifically" to MCH receptor if it binds to an MCH receptor (total binding minus nonspecific binding) with a K_i that is 10-fold, preferably 100-fold, and more preferably 1000-fold, less than the K_i measured for modulator binding to other G protein-coupled receptors.

A "prodrug" is a compound that may not fully satisfy the structural requirements of the compounds provided herein, but is modified *in vivo*, following administration to a patient, to produce a substituted 1-benzyl-1*H*-benzoimidazol-2-yl-methyl analogue. For example, a prodrug may be an acylated derivative of a compound as provided herein. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups within the compounds provided herein.

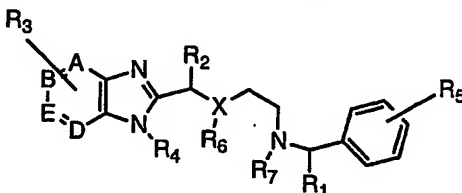
A "patient" is any individual treated with a MCH receptor modulator as provided herein. Patients include humans, as well as other animals such as companion animals and livestock. Patients may be afflicted with a condition associated with undesirable MCH receptor activation, or may be free of such a condition (*i.e.*, treatment may be prophylactic).

MELANIN CONCENTRATING HORMONE RECEPTOR MODULATORS

As noted above, the present invention provides melanin concentrating hormone (MCH) receptor modulators (*i.e.*, compounds that detectably modulate both MCH binding to MCH receptor and MCH-mediated signal transduction). Such modulators may be specific for a particular MCH receptor (*e.g.*, type 1 or type 2), or may inhibit or enhance ligand binding to multiple MCH receptors. MCH receptor modulators may be used to modulate MCH binding to MCH receptors *in vivo*, especially in the treatment of metabolic, feeding and sexual disorders in

humans, domesticated companion animals and livestock animals. Modulators may also be used within a variety of *in vitro* assays, such as assays for receptor activity, as probes for detection and localization of MCH receptors and as standards in assays of MCH binding and MCH-mediated signal transduction.

- 5 The MCH receptor modulators provided herein comprise active compounds that are multi-aryl (*i.e.*, have a plurality of unfused or fused aryl groups) and detectably modulate the binding of MCH to MCH receptor at nanomolar concentrations, preferably at subnanomolar concentrations. Active compounds provided herein are generally substituted 2-(4-benzyl-piperazin-1-ylmethyl)-1H-benzimidazole or 2-(4-benzyl-diazepan-1-ylmethyl)-1H-benzimidazole analogues, as defined above. Preferred compounds bind specifically, and with high affinity, to an MCH receptor. Without wishing to be bound to any particular theory, it is believed that the interaction of the compounds provided herein with an MCH receptor results in the MCH receptor modulating activity of these compounds. Active compounds include receptor agonists and antagonists.
- 10 15 The present invention is based, in part, on the discovery that small, amino acid-free molecules having the general Formula I (as well as pharmaceutically acceptable salts and prodrugs thereof) modulate MCH binding to MCH receptor.



Formula I

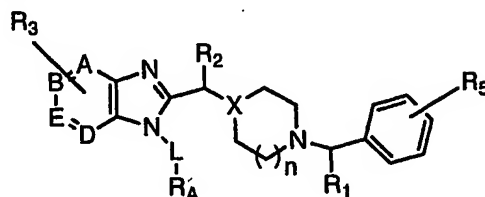
- 20 Within Formula I, variables are generally as described above. Within certain embodiments, A, B, E and D are all CH. R_1 and R_2 of Formula I are preferably independently hydrogen or C_1 - C_6 alkyl. If R_2 is halogen or hydroxy, then X is preferably CH. R_3 represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D (*i.e.*, any of A, B, E or D that is a nitrogen atom is not linked to an R_3 substituent). Preferably, R_3 at each of these positions is absent or C_1 - C_6 alkyl.
- 25 When R_4 is a carbocyclic or heterocyclic group having the formula $L-R_A$, L is a small alkyl linking unit (*i.e.*, C_1 - C_6 alkyl, preferably C_1 - C_4 alkyl, more preferably C_1 - C_2 alkyl), and R_A is a 5- to 7-membered carbocyclic or heterocyclic ring, optionally substituted as described above. Preferably, R_A is a six-membered ring; more preferably R_A is phenyl. Within particularly preferred embodiments, R_4 is benzyl, optionally substituted with from 1 to 3 substituents
- 30 independently selected from halogen, C_1 - C_6 alkyl, halo C_1 - C_6 alkyl, C_1 - C_6 alkoxy, and halo C_1 - C_6 alkoxy.

Certain R_5 groups include, *e.g.*, halogen, C_1 - C_6 alkyl, C_1 - C_6 alkoxy and dioxalane.

Within certain embodiments, as described above, R_6 and R_7 are joined to form, with XCH_2CH_2N , an optionally substituted 5- to 7-membered heterocyclic ring (*e.g.*, piperidinyl,

piperazinyl, hexamethylenimine or diazepanyl). If X is N, any heterocyclic ring formed is preferably 6- or 7-membered ring.

Certain such compounds satisfy Formula II, wherein n is 1 or 2 and all other variable positions are as described above.

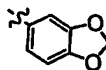


Formula II

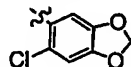
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Representative such compounds include, but are not limited to, those indicated in Tables I (below) and II (Example 1). R groups in Table I refer to Formula II, with the following abbreviations: Ph=phenyl; Naphth=naphthyl; Me=methyl; DiMe=dimethyl; MeO=methoxy; DiMe-dimethoxy; Imidz=imidazole; py=pyridine; pip=piperidine. 3,4-OCH₂O indicates dioxol.

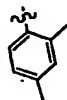
10 When R₅ is "3,4-OCH₂O," R₅ and the ring to which it is attached form the following group:



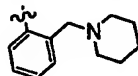
When R₅ is "6-Cl; 3,4-OCH₂O," R₅ and the ring to which it is attached form the group:



15 For compounds in which R_A is a substituted phenyl, substituent location is indicated in the conventional manner. For example, when L-R_A is 2,4-DiMePhCH₂-, L is -CH₂- and R_A has the structure:



Similarly, when L-R_A is 2-pipCH₂-PhCH₂-, L is -CH₂- and R_A has the structure:



20

Table I

X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
N	All C	H	H	none	4-BrPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
N	All C	H	H	none	2-FPhCH(CH ₃)-	3,4-OCH ₂ O	1
N	All C	H	H	none	Naphth-2ylCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
N	All C	H	H	none	3,4-DiMePhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	2-FPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2,5-DiMePhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-MeO	1

X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
N	All C	H	H	none	3,5-DiFPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	3,5-DiMeOPhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
N	All C	H	H	none	2,4-DiClPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	4-ClPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	4-BrPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	Me	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	Me	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	3-BrPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2,4-DiClPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	2,4-DiMePhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	4-(CF ₃)PhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	4-(CF ₃)PhCH ₂ -	2-F; 5-MeO	2
N	All C	H	H	none	3,4-DiMePhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	4-phenyl-PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
N	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-MeO	1
N	All C	H	H	none	3,5-DiMePhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	4-FPhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	PhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	Naphth-1ylCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-Br	1
N	All C	H	H	none	2-MePhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2-ClPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2-F,5-MeOPhCH ₂ -	3,4-OCH ₂ O	1
N	All C	H	H	none	2-FPhCH(CH ₃)-	2-F; 5-MeO	1
N	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 3-MeO	1
N	All C	H	H	none	2-MeOPhCH ₂ -	3,4-diF	2
N	All C	H	H	none	2-MeOPhCH ₂ -	4-Cl	2
N	All C	H	H	none	2-MeOPhCH ₂ -	4-Me	2
N	All C	H	H	none	2-MeOPhCH ₂ -	3,4 diMe	1
N	All C	H	H	none	2-MeOPhCH ₂ -	3,4 diMe	2
N	All C	H	H	none	2-MeOPhCH ₂ -	3-Me; 4-F	1
N	All C	H	H	none	2-MeOPhCH ₂ -	3-Me; 4-F	2
N	All C	H	H	none	2-MeOPhCH ₂ -	carbazole	2
N	All C	H	H	none	PhCH(CH ₃)-	3,4-OCH ₂ O	1
N	All C	H	H	none	PhCH(CH ₃)-	3,4-OCH ₂ O	2
N	All C	H	H	none	PhCH ₂ -	3,4 diF	1
N	All C	H	H	none	PhCH ₂ -	3,4 diF	2

X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
N	All C	H	H	none	4-PyCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	None	2,6-DiFPhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	5-CF ₃	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	none	2-pipCH ₂ -PhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	none	2,4-DiFPhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	none	2,5-DiFPhCH ₂ -	3,4-OCH ₂ O	2
N	B = N; others C	H	H	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
N	All C	H	H	none	3-PyCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	4-BrPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	4-BrPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
CH	All C	H	H	none	PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	2
CH	All C	H	H	none	2-FPhCH(CH ₃)-	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-FPhCH(CH ₃)-	3,4-OCH ₂ O	2
CH	All C	H	H	none	Naphth-2ylCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
CH	All C	H	H	none	Naphth-2ylCH ₂ -	6-Cl; 3,4-OCH ₂ O	2
CH	All C	H	H	none	3,4-DiMePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3,4-DiMePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	2-FPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-FPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,5-DiMeOPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3,5-DiMeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	PhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	PhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,5-DiFPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	3,5-DiFPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	3,5-DiMeOPhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
CH	All C	H	H	none	3,5-DiMeOPhCH ₂ -	6-Cl; 3,4-OCH ₂ O	2
CH	All C	H	H	none	2,4-DiClPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	2,4-DiClPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4-ClPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4-ClPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4-BrPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4-BrPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	1

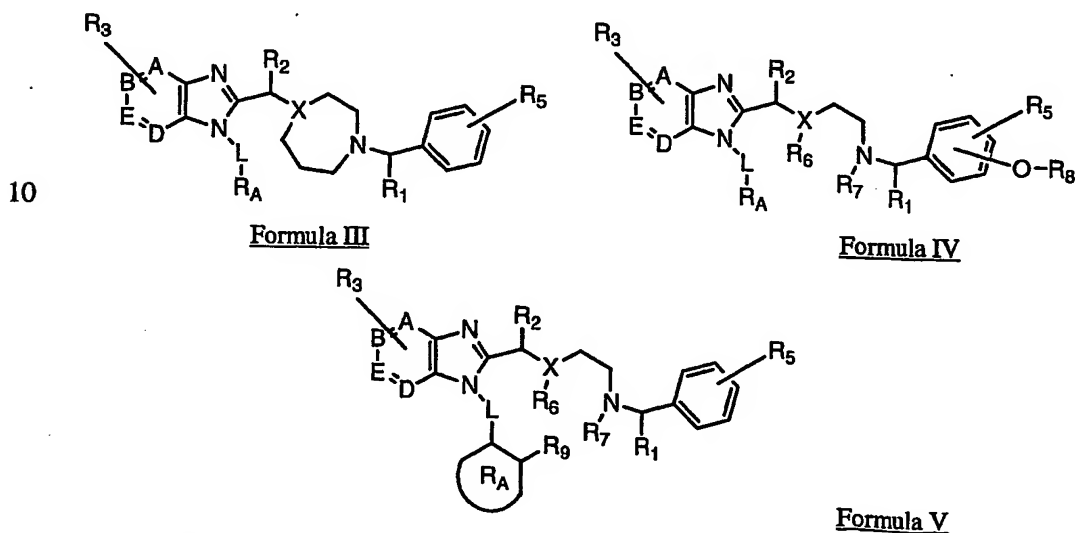
X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	Me	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	Me	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,5-DiMePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3,5-DiMePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	4-phenyl-PhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4-phenyl-PhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	3-BrPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3-BrPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3,5-(CF ₃) ₂ PhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2,4-DiClPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,4-DiClPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	2,4-DiMePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,4-DiMePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	4-(CF ₃)PhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4-(CF ₃)PhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4,5-DiMePhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4,5-DiMePhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4-phenyl-PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	1
CH	All C	H	H	none	4-phenyl-PhCH ₂ -	6-Cl; 3,4-OCH ₂ O	2
CH	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-MeO	1
CH	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-MeO	2
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	3,5-DiMePhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	3,5-DiMePhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	3,4-DiFPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	4-FPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	4-FPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	3-ClPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	PhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	PhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-Br	1

X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
CH	All C	H	H	none	Naphth-2ylCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	Naphth-1ylCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	Naphth-1ylCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	2,5-DiMePhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	4-isobutylPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	4-BrPhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	4-BrPhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	3,4-DiMePhCH ₂ -	2-F; 5-Br	1
CH	All C	H	H	none	3,4-DiMePhCH ₂ -	2-F; 5-Br	2
CH	All C	H	H	none	2-MePhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-MePhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-ClPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-ClPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-F,5-MeOPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-F,5-MeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-FPhCH(CH ₃)-	2-F; 5-MeO	1
CH	All C	H	H	none	2-FPhCH(CH ₃)-	2-F; 5-MeO	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	2-F; 3-MeO	2
CH	All C	H	H	none	PhCH ₂ -	3-MeO	1
CH	All C	H	H	none	PhCH ₂ -	3-MeO	2
CH	All C	H	H	none	2-FPhCH ₂ -	3-MeO	2
CH	All C	H	H	none	2-FPhCH ₂ -	3-MeO	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4-diF	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4-diF	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	4-Cl	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	4-Cl	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	4-Me	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	4-Me	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4 diMe	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	3,4 diMe	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	3-Me,4-F	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	3-Me,4-F	2
CH	All C	H	H	none	2-MeOPhCH ₂ -	carbazole	1
CH	All C	H	H	none	2-MeOPhCH ₂ -	carbazole	2
CH	All C	H	H	none	PhCH(CH ₃)-	3,4-OCH ₂ O	1
CH	All C	H	H	none	PhCH(CH ₃)-	3,4-OCH ₂ O	2
CH	All C	H	H	none	PhCH ₂ -	3,4 diF	1
CH	All C	H	H	none	PhCH ₂ -	3,4 diF	2
CH	All C	H	H	none	4-PyCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	4-PyCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2,6-DiFPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,6-DiFPhCH ₂ -	3,4-OCH ₂ O	2

X	A, B, E, D	R ₁	R ₂	R ₃	L-R _A	R ₅	n
CH	All C	H	H	5-CF ₃	2-MeOPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	5-CF ₃	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2-pipCH ₂ -PhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2-pipCH ₂ -PhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2,4-DiFPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,4-DiFPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	2,5-DiFPhCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	2,5-DiFPhCH ₂ -	3,4-OCH ₂ O	2
CH	B = N; others C	H	H	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	1
CH	B = N; others C	H	H	none	2-MeOPhCH ₂ -	3,4-OCH ₂ O	2
CH	All C	H	H	none	3-PyCH ₂ -	3,4-OCH ₂ O	1
CH	All C	H	H	none	3-PyCH ₂ -	3,4-OCH ₂ O	2

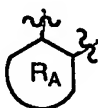
It will be apparent that the specific compounds recited herein are only representative examples of compounds provided herein, and are not intended to limit the scope of the present invention. As noted above, all compounds provided herein may be present as a hydrate, free base or as a pharmaceutically acceptable acid addition salt.

- 5 Within preferred embodiments, compounds provided herein satisfy one or more of Formulas III-V. It has been found, within the context of the present invention, that compounds in which R₆ and R₇ join to form a 7-membered ring may display a higher potency than those with a 6-membered ring. Accordingly, compounds of Formula III are particularly preferred in some instances.



Within Formulas III-V, A, B, E, D, X, R₁-R₇, L and R_A are as described above. R₈, of Formula IV, is hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₂-C₈alkanoyl, C₂-C₈alkyl

ether, haloC₁-C₈alkyl, haloC₁-C₈alkoxy or a substituent that is joined to R₅ to form a 5- or 6-membered heterocyclic ring such as dioxolane.



of Formula V is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl, haloC₁-C₈alkyl, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate and 5- to 10-membered carbocyclic and heterocyclic groups. R₉ of Formula V is hydroxy, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₂-C₈alkanoyloxy or haloC₂-C₈alkanoyloxy.

Substituted benzoimidazole analogues provided herein detectably alter (modulate) MCH binding to MCHR1 and/or MCHR2 receptor, as determined using a standard *in vitro* MCH receptor ligand binding assay and/or calcium mobilization assay. References herein to a "MCH receptor ligand binding assay" are intended to refer to a standard *in vitro* receptor binding assay as provided in Example 2. Briefly, a competition assay may be performed in which an MCH receptor preparation is incubated with labeled (*e.g.*, ¹²⁵I) MCH and unlabeled test compound. Within the assays provided herein, the MCH receptor used is preferably a mammalian MCHR1 or MCHR2 receptor, more preferably a human or monkey MCHR1 or MCHR2 receptor. The MCH receptor preparation may be, for example, a membrane preparation from HEK293 cells that recombinantly express a monkey MCH receptor (such as the MCHR1 sequence provided in SEQ ID NOs:1 and 2), human MCHR1 receptor (GenBank Accession No. AB063174), or human MCHR1/human beta-2-adrenergic receptor.

Incubation with a compound that detectably modulates MCH binding to MCH receptor will result in a decrease or increase in the amount of label bound to the MCH receptor preparation, relative to the amount of label bound in the absence of the compound. Preferably, such a compound will exhibit a K_i at an MCH receptor of less than 1 micromolar, more preferably less than 500 nM, 100 nM, 20 nM or 10 nM, within a MCH receptor ligand binding assay performed as described in Example 2. Generally preferred compounds are MCH receptor antagonists, and exhibit EC₅₀ values of about 4 micromolar or less, more preferably 1 micromolar or less, still more preferably about 100 nanomolar or less, 10 nanomolar or less or 1 nanomolar or less within a standard *in vitro* MCH receptor mediated calcium mobilization assay, as provided in Example 3.

In general, preferred compounds of the present invention do not substantially interact with dopamine receptors, particularly human dopamine D2 and D4 receptors. Dopamine receptor binding assays may be performed using standard methods, such as the assay described in

Example 4. Preferably, compounds exhibit K_i values greater than 1 micromolar within such an assay.

If desired, compounds provided herein may be evaluated for certain pharmacological properties including, but not limited to, oral bioavailability (preferred compounds are orally
5 bioavailable to an extent allowing for therapeutically effective concentrations of the compound to be achieved at oral doses of less than 140 mg/kg, preferably less than 50 mg/kg, more preferably less than 30 mg/kg, even more preferably less than 10 mg/kg, still more preferably less than 1 mg/kg and most preferably less than 0.1 mg/kg), toxicity (a preferred compound is nontoxic when a therapeutically effective amount is administered to a subject), side effects (a preferred
10 compound produces side effects comparable to placebo when a therapeutically effective amount of the compound is administered to a subject), serum protein binding and *in vitro* and *in vivo* half-life (a preferred compound exhibits an *in vitro* half-life that is equal to an *in vivo* half-life allowing for Q.I.D dosing, preferably T.I.D. dosing, more preferably B.I.D. dosing, and most preferably once-a-day dosing). In addition, differential penetration of the blood brain barrier
15 may be desirable for compounds used to treat CNS disorders, while low brain levels of compounds used to treat peripheral disorders may be preferred (*i.e.*, such doses do not provide brain (*e.g.*, CSF) levels of the compound sufficient to significantly modulate MCH receptor activity). Routine assays that are well known in the art may be used to assess these properties, and identify superior compounds for a particular use. For example, assays used to predict
20 bioavailability include transport across human intestinal cell monolayers, including Caco-2 cell monolayers. Penetration of the blood brain barrier of a compound in humans may be predicted from the brain levels of the compound in laboratory animals given the compound (*e.g.*, intravenously). Serum protein binding may be predicted from albumin binding assays. Such assays are described in a review by Oravcová, et al. (Journal of Chromatography B (1996)
25 volume 677, pages 1-27). Compound half-life is inversely proportional to the frequency of dosage of a compound. *In vitro* half-lives of compounds may be predicted from assays of microsomal half-life as described within Example 6, herein.

Toxicity and side effects may be assessed using any standard method. In general, the term "nontoxic" as used herein shall be understood in a relative sense and is intended to refer to
30 any substance that has been approved by the United States Food and Drug Administration ("FDA") for administration to mammals (preferably humans) or, in keeping with established criteria, is susceptible to approval by the FDA for administration to mammals (preferably humans). Toxicity may be also evaluated using the assay detecting an effect on cellular ATP production provided in Example 5. Other assays that may be used include bacterial reverse
35 mutation assays, such as an Ames test, as well as standard teratogenicity and tumorigenicity assays. Preferably, administration of compounds provided herein at certain doses (*i.e.*, doses yielding therapeutically effective *in vivo* concentrations or preferably doses of 0.01, 0.05, 0.1,

0.5, 1, 5, 10, 40, or 50 mg/kg administered parenterally or orally) does not result in prolongation of heart QT intervals (*i.e.*, as determined by electrocardiography in guinea pigs, minipigs or dogs). When administered daily for five or preferably ten days, such doses also do not cause liver enlargement resulting in an increase of liver to body weight ratio of more than 100%, preferably not more than 75% and more preferably not more than 50% over matched controls in laboratory rodents (*e.g.*, mice or rats). Such doses also preferably do not cause liver enlargement resulting in an increase of liver to body weight ratio of more than 50%, preferably not more than 25%, and more preferably not more than 10% over matched untreated controls in dogs or other non-rodent mammals.

Preferred compounds also do not promote substantial release of liver enzymes (*e.g.*, ALT, LDH, or AST) from hepatocytes *in vivo*. Preferably the above doses do not elevate serum levels of such enzymes by more than 100%, preferably not by more than 75% and more preferably not by more than 50% over matched untreated controls *in vivo* in laboratory rodents. Similarly, concentrations (in culture media or other such solutions that are contacted and incubated with cells *in vitro*) equivalent to two, fold, preferably five-fold, and most preferably ten-fold the minimum *in vivo* therapeutic concentration do not cause detectable release of any of such liver enzymes from hepatocytes *in vitro* into culture medium above baseline levels seen in media from untreated cells.

Preferred compounds further do not exhibit significant activity as sodium ion channel blockers, exhibiting less than 15 percent inhibition, and more preferably less than 10 percent inhibition, of sodium channel specific ligand (*e.g.*, batrachotoxin, tetrodotoxin or saxitoxin) binding when present at a concentration of 4 μ M or less. Assays for sodium channel specific ligand binding are well known in the art. In addition, preferred compounds do not exhibit significant androgen antagonist activity (*e.g.*, *in vivo*, in a Hershberger assay, or *in vitro*, in an assay such as that described by Nellemann et al. (2001) *Toxicology* 163(1):29-38). Preferred compounds exhibit less than a 15% inhibition, 10% inhibition or 5% inhibition of androgen receptor activation in the *in vitro* assay when present at concentrations of 4 μ M or less. By significant activity is meant results varying from control at the $p < 0.1$ level or more preferably at the $p < 0.05$ level of significance as measured using a standard parametric assay of statistical significance such as a student's T test.

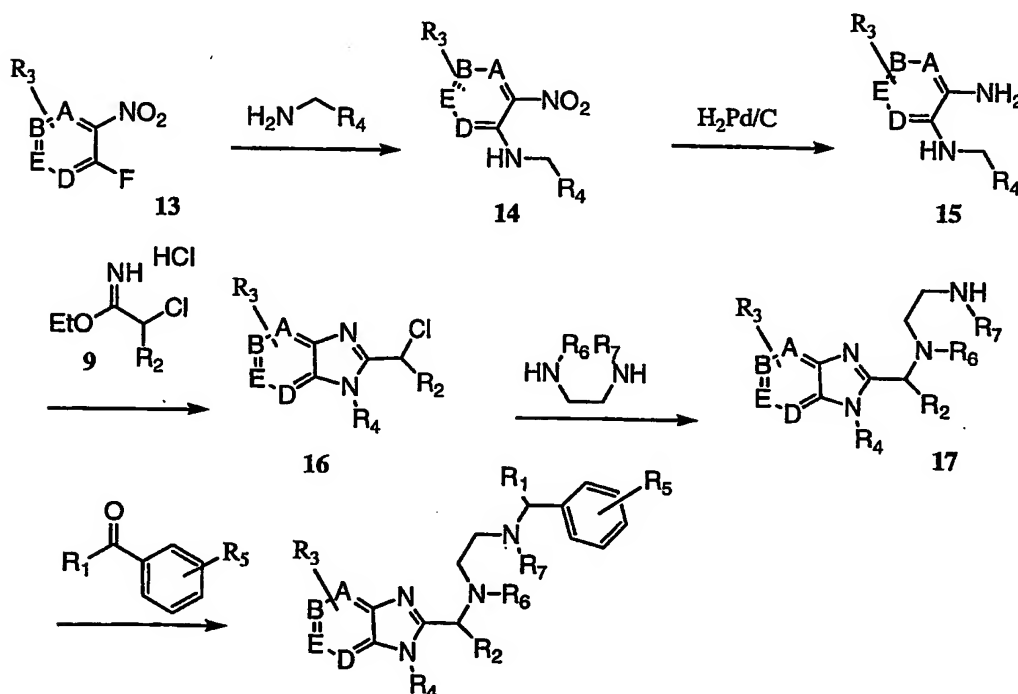
For detection purposes, as discussed in more detail below, compounds provided herein may be isotopically-labeled or radiolabeled. Accordingly, compounds recited in Formula I may have one or more atoms replaced by an atom of the same element having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be present in the compounds provided herein include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^2H , ^3H , ^{11}C , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{31}P , ^{32}P , ^{35}S , ^{18}F and ^{36}Cl . In addition, substitution with heavy isotopes such as

deuterium (*i.e.*, ^2H) can afford certain therapeutic advantages resulting from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements and, hence, may be preferred in some circumstances.

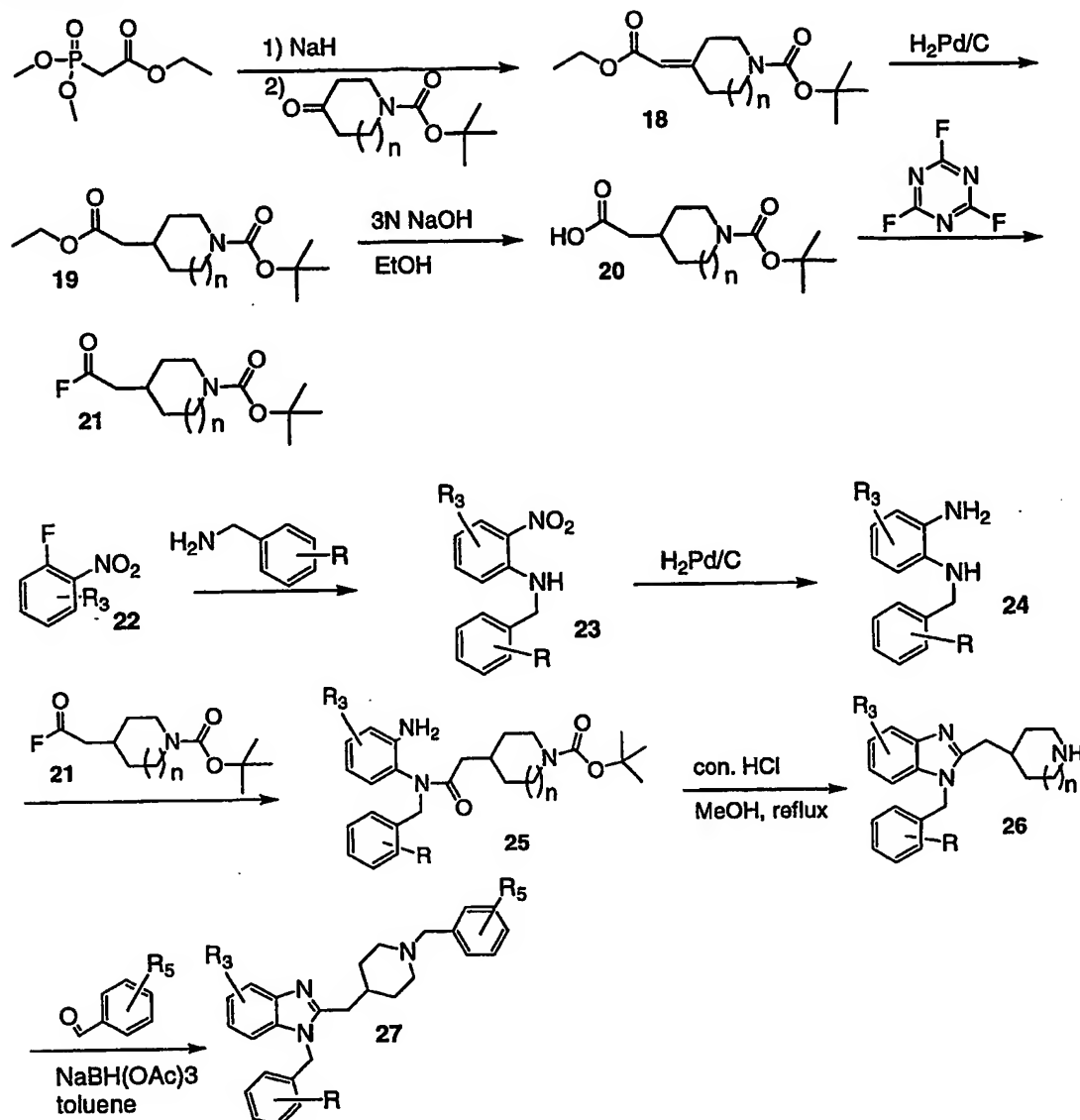
5 PREPARATION OF MCH RECEPTOR MODULATORS

Compounds provided herein may generally be prepared using standard synthetic methods. Starting materials are generally readily available from commercial sources, such as Sigma-Aldrich Corp. (St. Louis, MO). For example, a synthetic route similar to that shown in Scheme I may be used to prepare compounds of Formula I in which X is N. As shown in Scheme I, treatment of a compound of general formula 13 with an amine affords a compound of general formula 14. Reduction of a compound of general formula 14 followed by ring closure yields a compound of general formula 16. Treatment of a compound of general formula 16 with a diamine can afford a compound of general formula 17, which may then be treated with a substituted benzaldehyde to afford a compound of general formula I.

15 Scheme I:



20 Compounds of Formula I in which X is CH may be synthesized according to the procedure shown in Scheme II.

Scheme II:

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Ethyl dimethylphosphonoacetate is treated with sodium hydride and Boc-protected azaketone to yield the unsaturated ester 18, and hydrogenated to afford the hydrogenation product 19. Treatment with NaOH results in the carboxylic acid 20, which is treated with cyanuric to afford the acid fluoride 21.

1-Fluoro-2-nitrobenzene (optionally substituted) 22 is reacted with an appropriately substituted benzylamine, and then hydrogenated to yield a benzyl-substituted phenylenediamine 24. This compound is then treated with compound 21, followed by HCl, to yield the secondary amine 26. Compound 26 is treated with a substituted benzaldehyde and purified to yield the product compound 27.

Compounds provided herein may contain one or more asymmetric carbon atoms, so that the compounds can exist in different stereoisomeric forms. These compounds can be, for

example, racemates or optically active forms. As noted above, all stereoisomers are encompassed by the present invention. Nonetheless, it may be desirable to obtain single enantiomers (*i.e.*, optically active forms). Standard methods for preparing single enantiomers include asymmetric synthesis and resolution of the racemates. Resolution of the racemates can be accomplished, for example, by conventional methods such as crystallization in the presence of a resolving agent, or chromatography using, for example a chiral HPLC column.

As noted above, the present invention encompasses pharmaceutically acceptable salts of the compounds described herein. As used herein, a "pharmaceutically acceptable salt" is an acid or base salt that is generally considered in the art to be suitable for use in contact with the tissues of human beings or animals without excessive toxicity, irritation, allergic response, or other problem or complication. Such salts include mineral and organic acid salts of basic residues such as amines, as well as alkali or organic salts of acidic residues such as carboxylic acids. Specific pharmaceutical salts include, but are not limited to, salts of acids such as hydrochloric, phosphoric, hydrobromic, malic, glycolic, fumaric, sulfuric, sulfamic, sulfanilic, formic, toluenesulfonic, methanesulfonic, ethane disulfonic, 2-hydroxyethylsulfonic, nitric, benzoic, 2-acetoxybenzoic, citric, tartaric, lactic, stearic, salicylic, glutamic, ascorbic, pamoic, succinic, fumaric, maleic, propionic, hydroxymaleic, hydroiodic, phenylacetic, alkanolic such as acetic, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and the like. Similarly, pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium and ammonium. Those of ordinary skill in the art will recognize further pharmaceutically acceptable salts for the compounds provided herein, including those listed by *Remington's Pharmaceutical Sciences*, 17th ed., Mack Publishing Company, Easton, PA, p. 1418 (1985). Accordingly, the present disclosure should be construed to include all pharmaceutically acceptable salts of the compounds specifically recited.

A wide variety of synthetic procedures are available for the preparation of pharmaceutically acceptable salts. In general, a pharmaceutically acceptable salt can be synthesized from a parent compound that contains a basic or acidic moiety by any conventional chemical method. Briefly, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred.

Prodrugs of the compounds provided herein may be prepared by modifying functional groups present in the compounds in such a way that the modifications are cleaved to the parent compounds. Prodrugs include compounds wherein hydroxy, amine or sulfhydryl groups are bonded to any group that, when administered to a mammalian subject, cleaves to form a free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups

within the compounds provided herein. Preferred prodrugs include acylated derivatives. Those of ordinary skill in the art will recognize various synthetic methods that may be employed to prepare prodrugs of the compounds provided herein.

Compounds may be radiolabeled by carrying out their synthesis using precursors comprising at least one atom that is a radioisotope. The radioisotope is preferably selected from of at least one of carbon (preferably ^{14}C), hydrogen (preferably ^3H), sulfur (preferably ^{35}S), or iodine (preferably ^{125}I). Synthesis of such radiolabeled compounds may be conveniently performed by a radioisotope supplier specializing in custom synthesis of radiolabeled probe compounds, such as Amersham Corporation, Arlington Heights, IL; Cambridge Isotope Laboratories, Inc. Andover, MA; SRI International, Menlo Park, CA; Wizard Laboratories, West Sacramento, CA; ChemSyn Laboratories, Lexena, KS; American Radiolabeled Chemicals, Inc., St. Louis, MO; and Moravsek Biochemicals Inc., Brea, CA. Tritium labeled compounds are also conveniently prepared catalytically via platinum-catalyzed exchange in tritiated acetic acid, acid-catalyzed exchange in tritiated trifluoroacetic acid, or heterogeneous-catalyzed exchange with tritium gas. Such preparations are also conveniently carried out as a custom radiolabeling by any of the suppliers listed above using the compound as substrate. In addition, certain precursors may be subjected to tritium-halogen exchange with tritium gas, tritium gas reduction of unsaturated bonds, or reduction using sodium borotritide, as appropriate.

PHARMACEUTICAL COMPOSITIONS

The present invention also provides pharmaceutical compositions comprising a MCH receptor modulator as described herein, together with at least one physiologically acceptable carrier or excipient. Pharmaceutical compositions may comprise, for example, one or more of water, buffers (*e.g.*, neutral buffered saline or phosphate buffered saline), ethanol, mineral oil, vegetable oil, dimethylsulfoxide, carbohydrates (*e.g.*, glucose, mannose, sucrose or dextrans), mannitol, proteins, adjuvants, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione and/or preservatives.

If desired, other active ingredients may also be included. For example, compositions intended for the treatment of eating disorders, particularly obesity and bulimia nervosa, may further comprise leptin, a leptin receptor agonist, a melanocortin receptor 4 (MC4), sibutramine, dextenfluramine, a growth hormone secretagogue, a beta-3 agonist, a 5HT-2 agonist, an orexin antagonist, a neuropeptide Y_1 or Y_5 antagonist, a galanin antagonist, a CCK agonist, a GLP-1 agonist and/or a corticotropin-releasing hormone agonist.

Pharmaceutical compositions may be formulated for any appropriate manner of administration, including, for example, topical, oral, nasal, rectal or parenteral administration. The term parenteral as used herein includes subcutaneous, intradermal, intravascular (*e.g.*, intravenous), intramuscular, spinal, intracranial, intrathecal and intraperitoneal injection, as well as any similar injection or infusion technique. In certain embodiments, compositions in a form

suitable for oral delivery to humans or other animals (*e.g.*, companion animals such as dogs) are preferred. Such forms include, for example, tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs. Within yet other embodiments, compositions of the present invention may be formulated as a lyophilizate.

Compositions intended for oral use may further comprise one or more components such as sweetening agents, flavoring agents, coloring agents and/or preserving agents in order to provide appealing and palatable preparations. Tablets contain the active ingredient in admixture with physiologically acceptable excipients that are suitable for the manufacture of tablets. Such excipients include, for example, inert diluents (*e.g.*, calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate), granulating and disintegrating agents (*e.g.*, corn starch or alginic acid), binding agents (*e.g.*, starch, gelatin or acacia) and lubricating agents (*e.g.*, magnesium stearate, stearic acid or talc). The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent (*e.g.*, calcium carbonate, calcium phosphate or kaolin), or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium (*e.g.*, peanut oil, liquid paraffin or olive oil).

Aqueous suspensions comprise the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents (*e.g.*, sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia); and dispersing or wetting agents (*e.g.*, naturally-occurring phosphatides such as lecithin, condensation products of an alkylene oxide with fatty acids such as polyoxyethylene stearate, condensation products of ethylene oxide with long chain aliphatic alcohols such as heptadecaethyleneoxycetanol, condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides such as polyethylene sorbitan monooleate). Aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil (*e.g.*, arachis oil, olive oil, sesame oil or coconut oil) or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and/or flavoring agents may be

added to provide palatable oral preparations. Such suspension may be preserved by the addition of an anti-oxidant such as ascorbic acid.

5 Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, such as sweetening, flavoring and coloring agents, may also be present.

10 Pharmaceutical compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil (*e.g.*, olive oil or arachis oil) or a mineral oil (*e.g.*, liquid paraffin) or mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums (*e.g.*, gum acacia or gum tragacanth), naturally-occurring phosphatides (*e.g.*, soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol), anhydrides (*e.g.*, sorbitan monoleate) and condensation products of partial esters derived from fatty acids and hexitol with ethylene oxide (*e.g.*, polyoxyethylene sorbitan monoleate). The emulsions may also contain
15 sweetening and/or flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, such as glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also comprise one or more demulcents, preservatives, flavoring agents and/or coloring agents.

20 A pharmaceutical composition may be prepared as a sterile injectible aqueous or oleaginous suspension. The modulator, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Such a composition may be formulated according to the known art using suitable dispersing, wetting agents and/or suspending agents such as those mentioned above. Among the acceptable vehicles and solvents that may be employed are water, 1,3-butanediol, Ringer's solution and isotonic sodium chloride solution. In
25 addition, sterile, fixed oils may be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed, including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectible compositions, and adjuvants such as local anesthetics, preservatives and/or buffering agents can be dissolved in the vehicle.

30 Modulators may also be prepared in the form of suppositories (*e.g.*, for rectal administration). Such compositions can be prepared by mixing the drug with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Suitable excipients include, for example, cocoa butter and polyethylene glycols.

35 For administration to non-human animals, the composition may also be added to animal feed or drinking water. It may be convenient to formulate animal feed and drinking water compositions so that the animal takes in an appropriate quantity of the composition along with its

diet. It may also be convenient to present the composition as a premix for addition to feed or drinking water.

Pharmaceutical compositions may be formulated as sustained release formulations (*i.e.*, a formulation such as a capsule that effects a slow release of modulator following administration).
5 Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of modulator release. The amount of modulator contained within a sustained release formulation depends
10 upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Modulators are generally present within a pharmaceutical composition in a therapeutically effective amount. A therapeutically effective amount is an amount that results in a discernible patient benefit, such as increased healing of a disease or disorder associated with
15 pathogenic MCH receptor, as described herein. A preferred amount will result in a concentration in a body fluid (*e.g.*, blood, plasma, serum, CSF, synovial fluid, lymph, cellular interstitial fluid, tears or urine) that is sufficient to inhibit the binding of MCH to MCH receptor *in vitro*. Compositions providing dosage levels ranging from about 0.1 mg to about 140 mg per kilogram of body weight per day are generally preferred (about 0.5 mg to about 7 g per human
20 patient per day).

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending, for example, upon the patient being treated and the particular mode of administration. Dosage unit forms will generally contain between from about 1 mg to about 500 mg of an active ingredient. Optimal dosages may be established
25 using routine testing, and procedures that are well known in the art.

Pharmaceutical compositions may be packaged for treating disorders responsive to melanin concentrating hormone receptor modulation (*e.g.*, treatment of metabolic disorders such as diabetes, heart disease, stroke, eating disorders such as obesity or bulimia, or sexual disorders such as anorgasmic or psychogenic impotence). Packaged pharmaceutical compositions include
30 a container holding a therapeutically effective amount of at least one MCH receptor modulator as described herein and instructions (*e.g.*, labeling) indicating that the contained composition is to be used for treating a disorder responsive to MCH receptor modulation in the patient.

METHODS OF USE

MCH receptor modulators provided herein may be used as agonists or (preferably)
35 antagonists of MCH receptor(s) in a variety of contexts, both *in vitro* and *in vivo*. Within certain aspects, MCH receptor antagonists may be used to inhibit the binding of MCH receptor ligand (such as MCH) to MCH receptor *in vitro* or *in vivo*. In general, such methods comprise

contacting a MCH receptor with a sufficient amount of one or more MCH receptor modulators provided herein, in the presence of MCH receptor ligand in aqueous solution and under conditions otherwise suitable for binding of the ligand to MCH receptor. The MCH receptor may be present in solution or suspension (*e.g.*, in an isolated membrane preparation), in a cultured or isolated cell preparation or within a patient. Preferably, the MCH receptor is a MCHR1 receptor present in the hypothalamus. In general, the amount of MCH receptor antagonist contacted with the receptor should be sufficient to yield a concentration in the aqueous solution sufficient to inhibit MCH receptor ligand binding to MCH receptor *in vitro* within, for example, a binding assay as described in Example 2 and/or a calcium mobilization assay as described in Example 3.

Also provided herein are methods for modulating, preferably inhibiting, the signal-transducing activity of a MCH receptor. Such modulation may be achieved by contacting a MCH receptor (either *in vitro* or *in vivo* in a human or animal) with an effective amount of one or more MCH receptor modulators under conditions suitable for binding of the modulator(s) to the receptor. Preferably, within such methods, signal-transducing activity is inhibited by the modulator. The receptor may be present in solution or suspension, in a cultured or isolated cell preparation or within a patient. Modulation of signal transducing activity may be assessed by detecting an effect on calcium ion conductance (also referred to as calcium mobilization or flux). In general, an effective amount of MCH receptor modulator(s) is an amount sufficient to yield a concentration (in an aqueous solution that is in contact with the receptor) that is sufficient to modulate MCH receptor signal transducing activity *in vitro* within a calcium mobilization assay as described in Example 3. MCH receptor modulator(s) are preferably administered to a patient (*e.g.*, a human) orally or topically, and are present within at least one body fluid of the patient while modulating MCH receptor signal-transducing activity.

The present invention further provides methods for treating conditions responsive to MCH receptor modulation. Within the context of the present invention, the term "treatment" encompasses both disease-modifying treatment and symptomatic treatment, either of which may be prophylactic (*i.e.*, before the onset of symptoms, in order to prevent, delay or reduce the severity of symptoms) or therapeutic (*i.e.*, after the onset of symptoms, in order to reduce the severity and/or duration of symptoms). A condition is "responsive to MCH receptor modulation" if it is characterized by inappropriate activity of a MCH receptor (*i.e.*, is associated with pathogenic MCH receptor activity), regardless of the amount of MCH receptor ligand present locally, and/or if modulation of MCH receptor activity results in alleviation of the condition or a symptom thereof. Such conditions include, for example, metabolic disorders (such as diabetes), heart disease, stroke, eating disorders (such as obesity and bulimia nervosa), or sexual disorders such as anorgasmic or psychogenic impotence. These conditions may be diagnosed and monitored using criteria that have been established in the art. Patients may include humans,

domesticated companion animals (pets, such as dogs) and livestock animals, with dosages and treatment regimes as described above.

Treatment regimens may vary depending on the compound used and the particular condition to be treated. However, for treatment of most disorders, a dosage regimen (frequency of administration) of 4 times daily or less is preferred. For the treatment of eating disorders, including obesity, a dosage regimen of 1 or 2 times daily is particularly preferred. For the treatment of impotence a single dose that rapidly reaches effective concentrations is desirable. It will be understood, however, that the specific dose level and treatment regimen for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular disease undergoing therapy. In general, the use of the minimum dose that is sufficient to provide effective therapy is preferred. Patients may generally be monitored for therapeutic effectiveness using medical or veterinary criteria suitable for the condition being treated or prevented, which will be familiar to those of ordinary skill in the art.

Within separate aspects, the present invention provides a variety of *in vitro* uses for the compounds provided herein. For example, such compounds may be used as probes for the detection and localization of MCH receptors, in samples such as tissue sections, as positive controls in assays for receptor activity, as standards and reagents for determining the ability of a candidate agent to bind to MCH receptor, or as radiotracers for positron emission tomography (PET) imaging or for single photon emission computerized tomography (SPECT). Such assays can be used to characterize MCH receptors in living subjects.

Within methods for determining the presence or absence of MCH receptor in a sample, a sample may be incubated with a compound as provided herein under conditions that permit binding of the compound to MCH receptor. The amount of compound bound to MCH receptor in the sample is then detected. For example, a compound may be labeled using any of a variety of well known techniques (*e.g.*, radiolabeled with a radionuclide such as tritium, as described herein), and incubated with the sample (which may be, for example, a preparation of cultured cells, a tissue preparation or a fraction thereof). A suitable incubation time may generally be determined by assaying the level of binding that occurs over a period of time. Following incubation, unbound compound is removed, and bound compound detected using any method for the label employed (*e.g.*, autoradiography or scintillation counting for radiolabeled compounds; spectroscopic methods may be used to detect luminescent groups and fluorescent groups). As a control, a matched sample may be simultaneously contacted with radiolabeled compound and a greater amount of unlabeled compound. Unbound labeled and unlabeled compound is then removed in the same fashion, and bound label is detected. A greater amount of detectable label in the test sample than in the control indicates the presence of MCH receptor in the sample.

Detection assays, including receptor autoradiography (receptor mapping) of MCH receptors in cultured cells or tissue samples may be performed as described by Kuhar in sections 8.1.1 to 8.1.9 of Current Protocols in Pharmacology (1998) John Wiley & Sons, New York.

5 Modulators provided herein may also be used within a variety of well known cell separation methods. For example, modulators may be linked to the interior surface of a tissue culture plate or other support, for use in immobilizing and thereby isolating MCH-expressing cells for screens, assays and growth in culture. Modulators may also be used to facilitate cell identification and sorting *in vitro*, permitting the selection of cells expressing a MCH receptor. Preferably, the modulator(s) for use in such methods are labeled as described herein. Within one
10 preferred embodiment, a modulator linked to a fluorescent marker, such as fluorescein, is contacted with the cells, which are then analyzed (or isolated) by fluorescence activated cell sorting (FACS).

The following Examples are offered by way of illustration and not by way of limitation. Unless otherwise specified all reagents and solvent are of standard commercial grade and are
15 used without further purification.

EXAMPLES

20

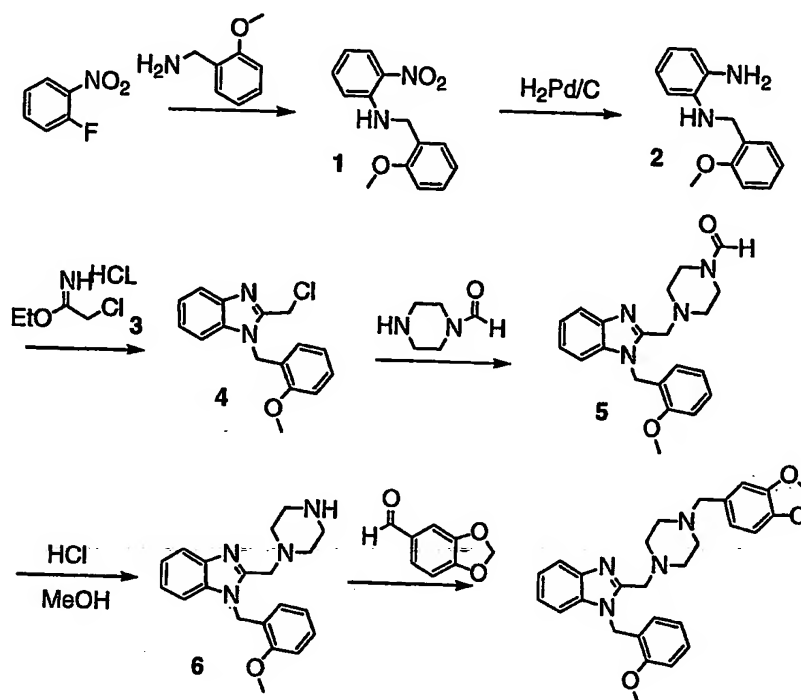
Example 1

Synthesis of Representative Compounds

This Example illustrates the preparation of representative MCH receptor modulators.

A. 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-benzimidazole

Scheme III



25 g (0.177 mole) of 1-Fluoro-2-nitrobenzene is added to a 500 ml round bottom flask containing a solution of 200 ml of anhydrous DMF and 24.28g (0.177 mole) of 2-Methoxybenzylamine. 73.27g (0.531 mole) of K₂CO₃ is added and the reaction mixture is stirred at room temperature for 3 hours. The reaction mixture is filtered through celite and washed with 400 ml of ethyl acetate. The filtrate is then washed twice with 200 mL saturated brine and twice with 200 mL water. The organic layer is dried over anhydrous Na₂SO₄ concentrated *in vacuo* to afford 32 g (0.13 mole, 76%) of (2-methoxy-benzyl)-(2-nitro-phenyl)-amine (1). ¹H NMR (400 MHz, DMSO) 8.6 (m, 1H), 8.0 (m, 1H), 7.4 (m, 1H), 7.2 (m, 2H), 7.0 (m, 1H), 6.8 (m, 2H), 6.6 (m, 1H) 4.6 (m, 2H), 3.8(s, 2H).

A solution of 32g (0.13 mole) of (2-methoxy-benzyl)-(2-nitro-phenyl)-amine (1) and 3.2 g Pd/C in 200 mL of 1:1 ethyl acetate:ethanol is treated at 40 psi of hydrogen for 1 hour. The reaction mixture is then filtered through celite and washed with 200 mL of ethanol. The solvent is then removed *in vacuo* to afford 28.2 g (0.12 mole, 92%) of N-(2-Methoxy-benzyl)-benzene-1,2-diamine (2).

In a 500 ml round bottom flask, a solution of 28.2 g (0.12 mole) of N-(2-Methoxy-benzyl)-benzene-1,2-diamine and 250 ml of anhydrous ethanol is treated with 45g (0.31 mole) of imidate 3 at room temperature for 2 hours. The solvent is removed *in vacuo*, and the residue is partitioned between ethyl acetate and saturated NaHCO₃. The organic layer is dried over anhydrous MgSO₄ and solvent is removed *in vacuo*. The resulting free base solid is diluted in

ethyl acetate and chromatographed on SiO₂ with 25% ethyl acetate/hexanes, and the HBr salt is made to afford 32.54 g (0.113 mole, 92%) of compound 4. LCMS MF = C₁₆H₁₅ClN₂O MW = 286.76 found 287 (M⁺). GCFID showed purity at 93.84%. ¹H NMR (300 MHz, DMSO) 7.6 (m, 1H), 7.4 (m, 1H), 7.2 (m, 3H), 7.0 (m, 1H), 6.79 (m, 2H), 5.5 (s, 2H), 5.1 (s, 2H), 3.8 (s, 3H).

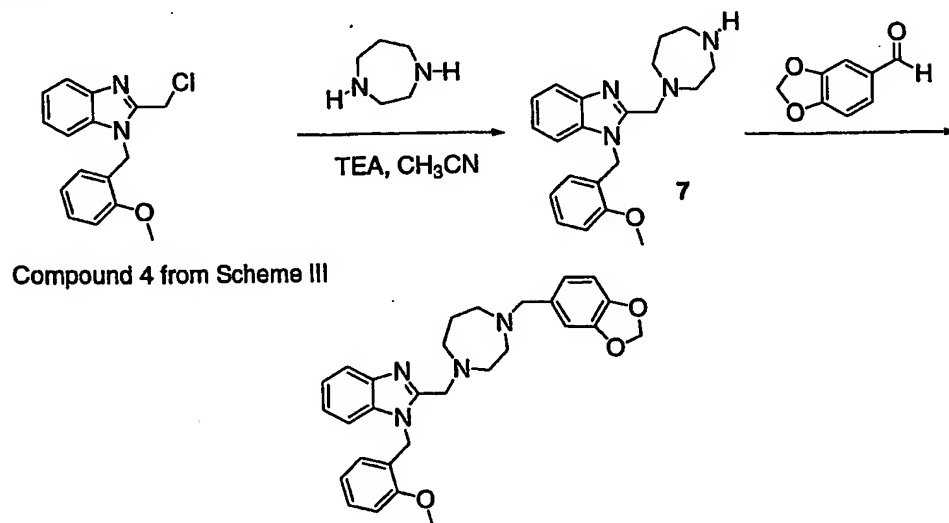
5 A solution of 2.0 g (0.007 mole) of 4 in 40 ml of acetonitrile and 10 ml TEA is treated with 1.20 g (0.011 mole) of N-Formylpiperazine and stirred at room temperature overnight. The solvent is removed in vacuo and the residue is partitioned between ethyl acetate and 1N NaOH. The organic layer is dried over anhydrous MgSO₄ and solvent is removed in vacuo to afford 1.70g (0.005 mole) of 5. 1.7 g of 5 is dissolved in 40 mL of methanol and 10 ml of concentrated
10 HCl is added. The resulting mixture is stirred at room temperature for 1 hour. The solvent is removed and the residue is partitioned between ethyl acetate and 10% acetic acid. The pH of the aqueous layer is adjusted to pH = 11 with 1N NaOH. The mixture is extracted with ethyl acetate and the organic layer is dried over anhydrous MgSO₄ and concentrated to afford 2.01g (0.06 mole, 85%) of 6.

15 A solution of 400 mg (0.0012 mole) of compound 6 in 10 mL of toluene is treated with 4 drops of acetic acid and 196 mg (0.0013 mole) of piperonal and 377 mg (0.0017 mole) of NaBH(OAc)₃ and stirred under N₂ at 50°C overnight. The resulting solution is partitioned between ethyl acetate and saturated NaHCO₃. The organic layer is dried over MgSO₄ and solvent is removed to afford a viscous oil. The di-HCl salt is made to afford 548 mg (0.0011 mole) of the
20 title compound. LCMS MF = C₂₈H₃₀N₄O₃ MW = 470.57 found 471 (M⁺). ¹H NMR (300 MHz, DMSO) 7.8 (m, 1H), 7.6 (s, 1H), 7.4 (m, 3H), 7.2 (s, 1H) 7.0 (m, 3H), 6.9 (m, 2H), 6.1 (s, 2H), 5.6 (s, 2H), 4.2 (m, 4H), 3.79 (s, 3H), 3.4 (m, 4H), 3.0 (m, 2H), 2.5 (s, 2H), 2.0 (m, 2H).

B. 2-(4-benzof[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-

25 1H-benzoimidazole

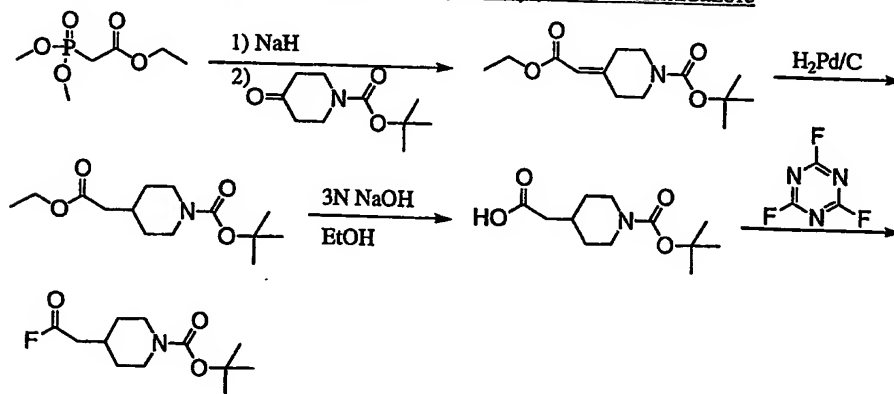
Scheme IV



Homopiperazine (6.5g, 6.5mmol) and triethylamine (18 mL, 130mmol) are dissolved in 20 mL acetonitrile at room temperature. Compound 4 (3.9g, 13mmol), suspended in 20 mL acetonitrile is added in portions and the heterogeneous reaction mixture is stirred for 15 hours. The solvent is removed *in vacuo* and the residue suspended in ethyl acetate, transferred to a separatory funnel and washed with 1 N NaOH followed by brine. The organic solution is dried over sodium sulfate, filtered, and evaporated to dryness to afford 4.5 g of a crude mixture containing 7 contaminated with a small amount of bis-alkylation product. This material is used without purification

To a solution of 7 (290 mg, 0.8 mmol) and piperonaldehyde (144 mg, 0.96 mmol) in 20 mL THF is added acetic acid (92 μ L, 1.6 mmol) followed by sodium triacetoxyborohydride (270 mg, 1.27 mmol). The reaction mixture is stirred at room temperature overnight. After quenching by addition of 1 N NaOH, the mixture is transferred to a separatory funnel and washed with brine. The organic phase is dried over sodium sulfate, filtered, and evaporated to dryness. The resulting oil is purified by preparative TLC eluting with 10/2/1 ethyl acetate / methanol / triethylamine to afford 150 mg of the title compound. ^1H NMR (300 MHz, CDCl_3) 7.78 (br d, 1H, $J = 6\text{Hz}$), 7.23 (m, 4H), 6.89 (d, 1H, $J = 6\text{Hz}$), 6.85 (s, 1H), 6.76 (t, 1H, $J = 6\text{Hz}$), 6.71 (s, 1H), 6.59 (d, 1H, $J = 6\text{Hz}$), 5.91 (s, 1H), 5.61 (s, 1H), 3.87 (m, 5H), 3.47 (s, 2H), 2.75-2.67 (m, 4H), 2.60-2.52 (m, 4H), 1.69 (m, 2H).

C. 1-Benzyl-2-(1-benzyl-piperidin-4-ylmethyl)-1H-benzimidazole



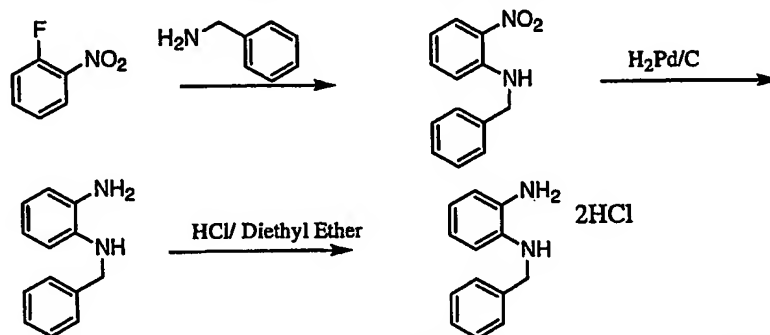
A 2L three neck round bottom flask is charged with of ethyl dimethylphosphonoacetate and 750ml of anhydrous THF while stirring under N_2 atmosphere at 0°C . Sodium hydride (1.1 equivalents, 60% in dispersion oil) is slowly added and the mixture is stirred for 1.5 hours. Boc-protected piperidin-4-one (0.9 equivalents) is added all at once. The reaction mixture is allowed to warm to room temperature and stirred overnight. The reaction mixture is quenched with saturated NaHCO_3 and transferred to a separatory funnel. The organic phase is removed and the aqueous phase is washed three times with ethyl acetate. The organic layers are combined and washed two times with brine. The organic layer is then dried over anhydrous MgSO_4 and

vacuum filtered. The filtrate is concentrated under reduced pressure to afford the unsaturated ester.

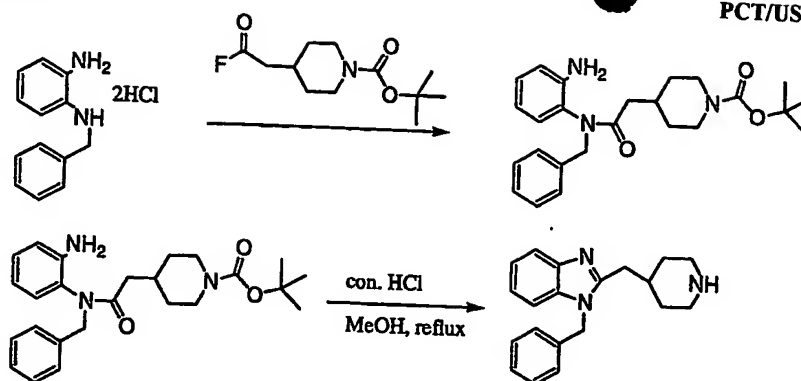
To a solution of the unsaturated ester in ethanol is added 10% Pd/C. The reaction mixture is subjected to hydrogenation at 35 psi for three hours. The reaction mixture is filtered through Celite and the filter cake is washed with ethanol. The filtrate is concentrated under reduced pressure to afford the hydrogenation product.

To a solution of the hydrogenation product in ethanol is added 3N NaOH (2.5 equivalents). The reaction mixture is heated to 60°C overnight. The reaction mixture is cooled to room temperature and concentrated in vacuo. The residue is adjusted to pH ~4 by addition of 10% HOAc. The resulting solution is extracted two times with ethyl acetate. The combined organic extracts are washed with brine then dried over Na₂SO₄. The extracts are filtered and concentrated under reduced pressure to obtain the carboxylic acid as a white solid.

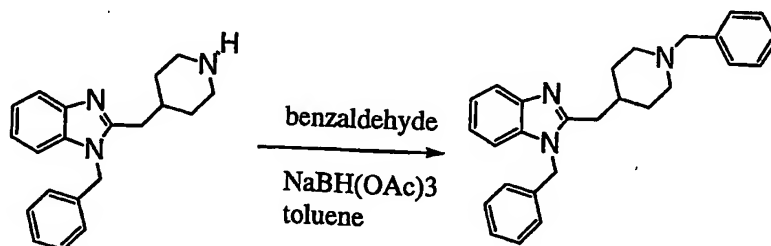
The acid is dissolved in acetonitrile. Diisopropylethylamine (1.5 equivalents) is added and the solution is stirred at room temperature for 20 minutes. Cyanuric Fluoride (1.1 equivalents) is added dropwise and the reaction is stirred overnight. The reaction mixture is poured over cold water and ethyl acetate is added. The mixture is transferred to a separatory funnel and the aqueous phase removed. The organic layer is washed two times with cold water and one time with brine. The organic phase is dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford the acid fluoride as a yellow solid.



1-Fluoro-2-nitrobenzene is dissolved in DMF at room temperature. Potassium carbonate (3 equivalents) is added followed by 1 equivalent of benzylamine. The reaction mixture is stirred at room temperature for three hours. The reaction mixture is vacuum filtered through Celite. The filter cake is washed with ethyl acetate. The filtrate is transferred to a separatory funnel and washed one time with cold water and three times with brine. The organic layer is dried over anhydrous Na₂SO₄ and removed *in vacuo* to obtain an orange solid. The solid is dissolved in 1:1 ethyl acetate/ethanol to which is added 10% Pd/C. The reaction mixture is subjected to hydrogenation at 40 psi for 1 hour. The reaction is then vacuum filtered through Celite and washed with 100ml of the solvent mixture. The solvent is removed *in vacuo*. The product, N-benzyl-benzene-1,2-diamine, is purified as its dihydrochloride salt by precipitation from HCl/ether.



- To 65ml of anhydrous acetonitrile is added N-benzyl-benzene-1,2-diamine (16mmol) and DIEA (48mmol). The reaction mixture is stirred 10 minutes under N_2 . Acid fluoride (16mmol) is added slowly and the reaction mixture is stirred overnight. The reaction mixture is diluted with ethyl acetate and transferred to a separatory funnel. The reaction mixture is washed once with 1N NaOH and then once with brine. The organic layer is dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The resulting solid is purified by silica gel chromatography eluting with dichloromethane followed by ethyl acetate to afford the anilide as a solid.
- 10 This solid compound is dissolved in anhydrous MeOH, and 35ml of concentrated HCl is added. The reaction mixture is heated at reflux for 12 hours. The reaction mixture is cooled to room temperature and concentrated under reduced pressure. The resulting oil is dissolved in water. The pH is adjusted to 11 with 10N NaOH. The resulting solution is transferred to a separatory funnel and extracted with ethyl acetate. The organic extract is dried over anhydrous $MgSO_4$ and the solvent is removed under reduced pressure. The residue is purified by flash chromatography eluting with ethyl acetate followed by 1N NH_3 in MeOH to afford the secondary amine.



- To a solution of the secondary amine (0.02 mmol) dissolved in 0.1 mL of toluene is added benzaldehyde (0.03 mmol) dissolved in toluene (0.15 mL), sodium triacetoxyborohydride (0.1 mmol) and acetic acid (0.1 mL of a solution made by dissolving 0.175 mL acetic acid in 10 mL toluene). The reaction mixture is heated for 16 hours at 50°C. After cooling to room temperature, the reaction mixture is quenched by addition of 0.5 mL 1 N NaOH. The reaction mixture is extracted with 0.5 mL ethyl acetate. The organic phase is delivered to a 1 g SCX ion

exchange column. The product is purified by elution with 2 mL methanol followed by 2N ammonia in methanol to afford 1-benzyl-2-(1-benzyl-piperidin-4-ylmethyl)-1*H*-benzoimidazole.

By readily apparent variation, compounds with the above general structure, but comprising R_A substituent(s) and/or R₅ group(s), are prepared.

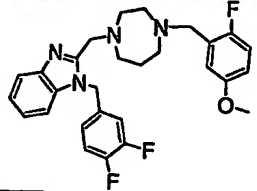
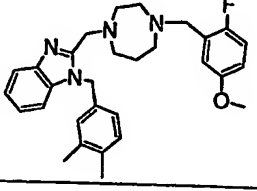
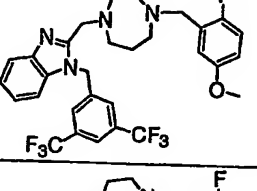
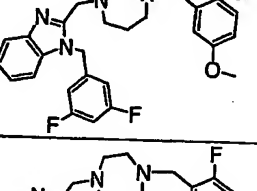
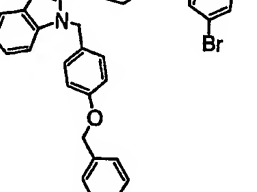
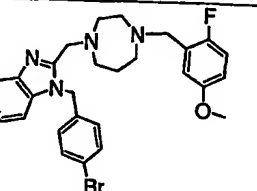
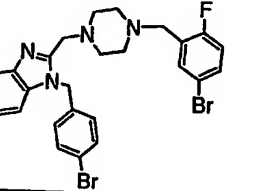
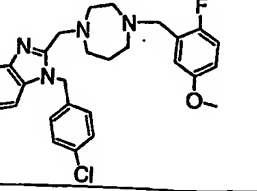
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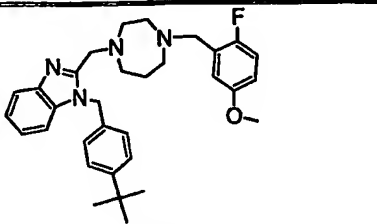
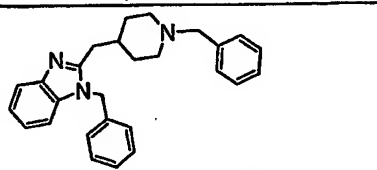
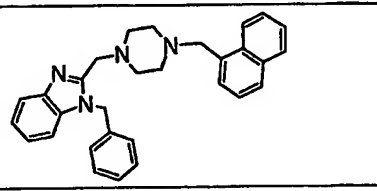
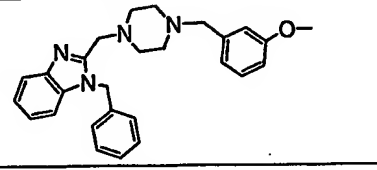
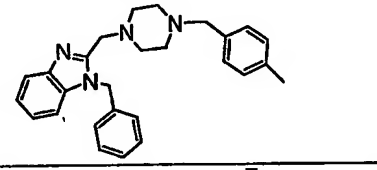
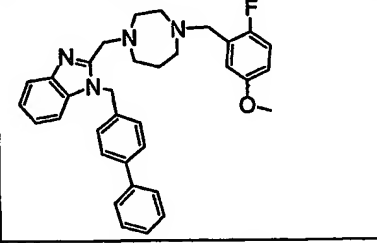
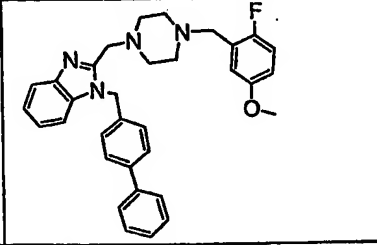
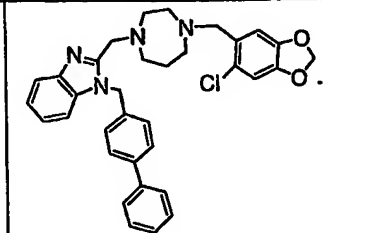
D. Additional compounds

By readily apparent variation of the above methods, the following compounds were prepared:

Table II

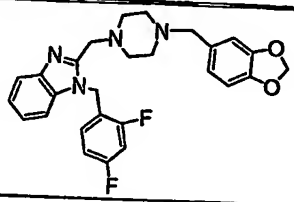
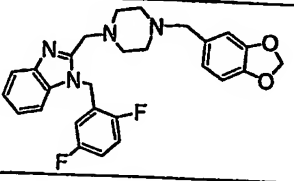
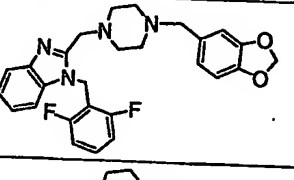
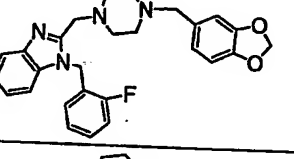
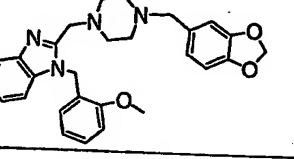
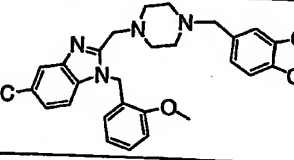
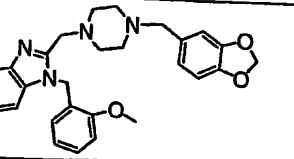
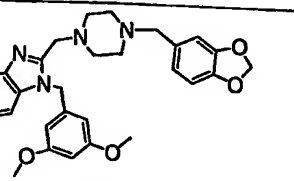
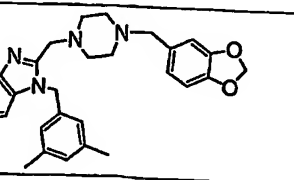
	Compound	Name
1.		1-(2,4-dichloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1 <i>H</i> -benzoimidazole
2.		1-(2,5-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1 <i>H</i> -benzoimidazole
3.		1-(2-chloro-benzyl)-2-[4-(2,4-dimethyl-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
4.		1-(2-fluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
5.		1-(2-fluoro-benzyl)-2-[4-(3-methoxy-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
6.		1-(2-fluoro-benzyl)-2-[4-(4-methyl-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
7.		1-(2-methoxy-benzyl)-2-[4-(naphthalen-1-ylmethyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole

8.	Compound	Name
		1-(3,4-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(3,4-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(3,5-bis-trifluoromethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(3,5-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(4-benzyloxy-benzyl)-2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(4-bromo-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole
		1-(4-Bromo-benzyl)-2-[4-(5-bromo-2-fluoro-benzyl)-piperazin-1-ylmethyl]-1H-benzoimidazole
		1-(4-chloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole

	Compound	Name
16.		1-(4- <i>tert</i> -butyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1 <i>H</i> -benzoimidazole
17.		1-benzyl-2-(1-benzyl-piperidin-4-ylmethyl)-1 <i>H</i> -benzoimidazole
18.		1-Benzyl-2-(4-naphthalen-1-ylmethyl-piperazin-1-ylmethyl)-1 <i>H</i> -benzoimidazole
19.		1-benzyl-2-[4-(3-methoxy-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
20.		1-Benzyl-2-[4-(4-methyl-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
21.		1-biphenyl-4-ylmethyl-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1 <i>H</i> -benzoimidazole
22.		1-Biphenyl-4-ylmethyl-2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1 <i>H</i> -benzoimidazole
23.		1-biphenyl-4-ylmethyl-2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1 <i>H</i> -benzoimidazole

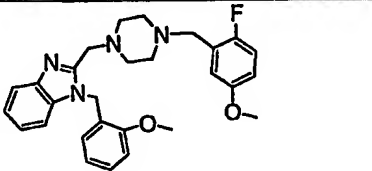
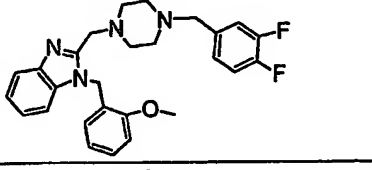
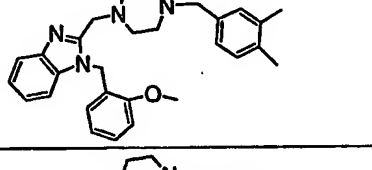
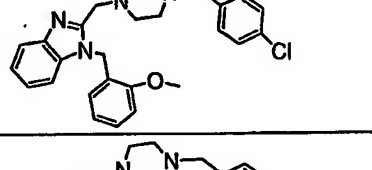
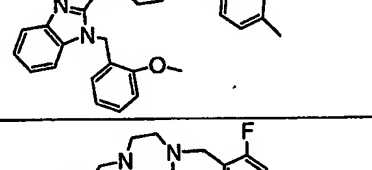
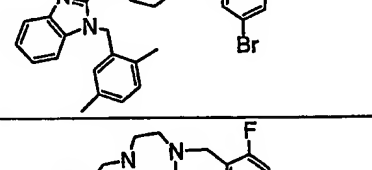
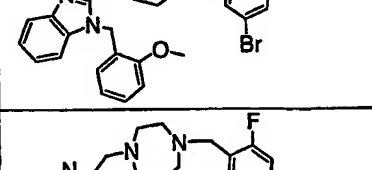
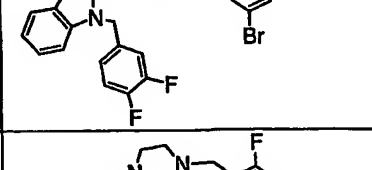
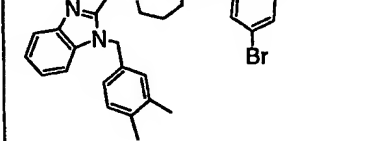
	Compound	Name
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25.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-benzoimidazole
26.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2,4-dichloro-benzyl)-1H-benzoimidazole
27.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2,4-dimethyl-benzyl)-1H-benzoimidazole
28.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2,5-dimethyl-benzyl)-1H-benzoimidazole
29.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2-bromo-benzyl)-1H-benzoimidazole
30.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2-chloro-benzyl)-1H-benzoimidazole
31.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2-fluoro-benzyl)-1H-benzoimidazole
32.		2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-(2-fluoro-5-methoxy-benzyl)-1H-benzoimidazole

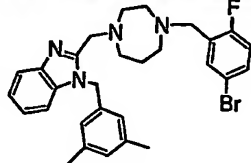
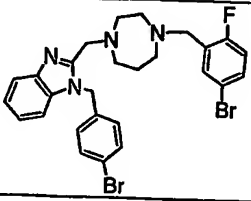
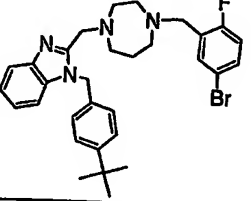
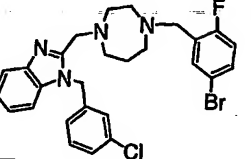
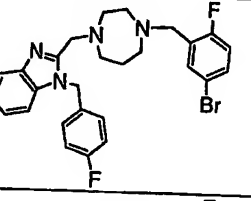
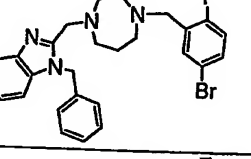
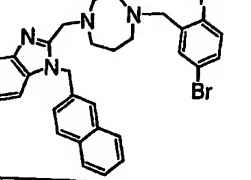
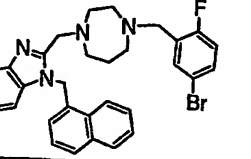
	Compound	Name
33.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-methyl-benzyl)-1H-benzoimidazole
34.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,4-dimethyl-benzyl)-1H-benzoimidazole
35.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-dimethoxy-benzyl)-1H-benzoimidazole
36.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-dimethyl-benzyl)-1H-benzoimidazole
37.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-bis-trifluoromethyl-benzyl)-1H-benzoimidazole
38.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-bromo-benzyl)-1H-benzoimidazole
39.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-[1-(2-fluoro-phenyl)-ethyl]-1H-benzoimidazole
40.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-benzyl-1H-benzoimidazole
41.		2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-tert-Butyl-benzyl)-1H-benzoimidazole

Compound	Name
42. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,4-difluoro-benzyl)-1H-benzimidazole
43. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,5-difluoro-benzyl)-1H-benzimidazole
44. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,6-difluoro-benzyl)-1H-benzimidazole
45. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-fluoro-benzyl)-1H-benzimidazole
46. 	2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-benzimidazole
47. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-5-trifluoromethyl-1H-benzimidazole
48. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-imidazo[4,5-c]pyridine
49. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(3,5-dimethoxy-benzyl)-1H-benzimidazole
50. 	2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(3,5-dimethyl-benzyl)-1H-benzimidazole

	Compound	Name
51.		2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(4-piperidin-1-ylmethyl-benzyl)-1H-benzoimidazole
52.		2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-[1-phenyl-ethyl]-1H-benzoimidazole
53.		2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-benzyl-1H-benzoimidazole
54.		2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1H-benzoimidazole
55.		2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-pyridin-4-ylmethyl-1H-benzoimidazole
56.		2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-pyridin-3-ylmethyl-1H-benzoimidazole
57.		2-[1-(2-fluoro-5-methoxybenzyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
58.		2-[1-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-ethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
59.		2-[1-(4-fluoro-3-methoxybenzyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole

	Compound	Name
60.		2-[1-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-piperidin-4-ylmethyl]-1-(2-fluoro-benzyl)-1H-benzoimidazole
61.		2-[1-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
62.		2-[4-(1-Benzo[1,3]dioxol-5-yl-ethyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
63.		2-[4-(2-fluoro-3-methoxy-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
64.		2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole
65.		2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-chloro-benzyl)-1H-benzoimidazole
66.		2-[4-(2-Fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-trifluoromethyl-benzyl)-1H-benzoimidazole
67.		2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-[1-(2-fluoro-phenyl)-ethyl]-1H-benzoimidazole
68.		2-[4-(2-Fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-1-ylmethyl-1H-benzoimidazole

	Compound	Name
69.		2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
70.		2-[4-(3,4-difluoro-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
71.		2-[4-(3,4-dimethyl-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
72.		2-[4-(4-chloro-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
73.		2-[4-(4-methyl-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
74.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2,5-dimethyl-benzyl)-1H-benzimidazole
75.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzimidazole
76.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,4-difluoro-benzyl)-1H-benzimidazole
77.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,4-dimethyl-benzyl)-1H-benzimidazole

78.	Compound	Name
		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,5-dimethyl-benzyl)-1H-benzoimidazole
79.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4-bromo-benzyl)-1H-benzoimidazole
80.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4- <i>tert</i> -butyl-benzyl)-1H-benzoimidazole
81.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-chloro-benzyl)-1H-benzoimidazole
82.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4-fluoro-benzyl)-1H-benzoimidazole
83.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-benzyl-1H-benzoimidazole
84.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-2-ylmethyl-1H-benzoimidazole
85.		2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-1-ylmethyl-1H-benzoimidazole

	Compound	Name
86.		2-[4-(5-Bromo-2-fluoro-benzyl)-piperazin-1-ylmethyl]-1-(2,5-dimethyl-benzyl)-1H-benzoimidazole
87.		2-[4-(5-Bromo-2-fluoro-benzyl)-piperazin-1-ylmethyl]-1-(3,4-dimethyl-benzyl)-1H-benzoimidazole
88.		2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-benzyl-1H-benzoimidazole
89.		2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-(3,5-dimethoxy-benzyl)-1H-benzoimidazole
90.		2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-piperazin-1-ylmethyl]-1-(2-fluoro-benzyl)-1H-benzoimidazole
91.		9-Ethyl-3-{4-[1-(2-methoxy-benzyl)-1H-benzoimidazol-2-ylmethyl]-piperazin-1-ylmethyl}-9H-carbazole

Example 2

Melanin Concentrating Hormone Receptor Binding Assay

5 This Example illustrates a standard assay of MCH receptor binding that may be used to determine the binding affinity of compounds for the MCH receptor.

Total RNA was prepared from Cynomolgus macaque hypothalamus. Monkey hypothalamic cDNA was prepared using random primers and reverse transcriptase according to standard methods. A cDNA encoding the monkey MCH1 receptor was obtained via PCR
 10 amplification using the forward (5') Primer of SEQ ID NO:3 and the reverse (3') Primer of SEQ ID NO:4. The full length PCR product was initially cloned into the vector pCR 2.1 (Invitrogen, Carlsbad, CA). The cDNA was reamplified using a forward primer engineered to include an optimal translation initiation site (Kozak sequence). A cDNA expression cassette fragment encoding the monkey MCH1 receptor was blunt end ligated into the PCR-SCRIPT vector

(STRATAGENE, La Jolla, CA). The receptor sequence was excised from this vector using EcoRI and Not I and subcloned into the EcoRI/Not site of PCDNA3.1 (INVITROGEN Corp., Carlsbad, CA). The MCH1 receptor DNA sequence is provided in SEQ ID NO:1, with the encoded amino acid sequence provided in SEQ ID NO:2.

5 HEK 293 cells (American Type Culture Collection, Manassas, VA) were stably transfected with the MCH receptor expression vector via standard calcium phosphate precipitation, and were grown to confluency (approximately 48-72 hours) in DMEM high glucose culture medium (catalog #10-017-CV, MEDiatech, Herndon, VA) supplemented with 10% fetal bovine serum and 25 mM HEPES, and 500 µg/ml G418, for 48-72 hours at 37°C, 5% CO₂. The cells were pelleted by gentle centrifugation. Cell pellets were washed twice with cold 10 PBS, harvested in cold PBS containing 5 mM EDTA, and stored at -80°C.

At the time of assay, pellets were thawed by addition of wash buffer (25 mM Hepes with 1.0 mM CaCl₂, 5.0 mM MgCl₂, 120 mM NaCl, PH7.4) and homogenized for 30 seconds using a BRINKMAN POLYTRON, setting 5. Cells were centrifuged for 10 minutes at 48,000 x g. The 15 supernatant was discarded and the pellet was resuspended in fresh wash buffer, and homogenized again. An aliquot of this membrane homogenate was used to determine protein concentration via the Bradford method (BIO-RAD Protein Assay Kit, #500-0001, BIO-RAD, Hercules, CA). By this measure, a 1-liter culture of cells typically yields 50-75 mg of total membrane protein. The homogenate was centrifuged as before and resuspended to a protein concentration of 333 µg/ml 20 in binding buffer (Wash buffer + 0.1% BSA and 1.0µM final phosphoramidon) for an assay volume of 50µg membrane protein/150ul binding buffer. Phosphoramidon was from SIGMA BIOCHEMICALS, St. Louis, MO (cat# R-7385).

Competition binding assays were performed at room temperature in Falcon 96 well round bottom polypropylene plates. Each assay well contained 150 µl of MCH receptor 25 containing membranes prepared as described above, 50 µl ¹²⁵I-Tyr MCH, 50 µl binding buffer, and 2 µl test compound in DMSO. ¹²⁵I-Tyr MCH (specific activity = 2200 Ci/mMol) is purchased from NEN, Boston, MA (Cat # NEX 373) and was diluted in binding buffer to provide a final assay concentration of 30 pM.

Non-specific binding was defined as the binding measured in the presence of 1 µM 30 unlabeled MCH. MCH is purchased from BACHEM U.S.A., King of Prussia, PA (cat # H-1482). Assay wells used to determine MCH binding contained 150 µl of MCH receptor containing membranes, 50 µl ¹²⁵I-Tyr MCH, 25 µl binding buffer, and 25 µl binding buffer.

Assay plates were incubated for 1 hour at room temperature. Membranes were harvested onto WALLAC™ glass fiber filters (PERKIN-ELMER, Gaithersburg, MD) which were pre-soaked with 1.0% PEI (polyethyleneimine) for 2 hours prior to use. Filters were allowed to dry 35 overnight, and then counted in a WALLAC 1205 BETA PLATE counter after addition of WALLAC BETA SCINT™ scintillation fluid.

For saturation binding, the concentration of ^{125}I -Tyr MCH was varied from 7 to 1,000 pM. Typically, 11 concentration points were collected per saturation binding curve. Equilibrium binding parameters were determined by fitting the allosteric Hill equation to the measured values with the aid of the computer program FitPTM (BIOSOFT, Ferguson, MO). For the compounds described herein, K_i values were below 1 micromolar, preferably below 500 nanomolar, more preferably below 100 nanomolar.

Example 3

Calcium Mobilization Assay

10 This Example illustrates a representative functional assay for monitoring the response of cells expressing MCH receptors to MCH. This assay can also be used to determine if test compounds act as agonists or antagonists of melanin concentrating hormone receptors.

Chinese Hamster Ovary (CHO) cells (American Type Culture Collection; Manassas, VA) were stably transfected with the MCH expression vector described in Example 2 via calcium phosphate precipitation, and were grown to a density of 15,000 cells/well in FALCONTM black-walled, clear-bottomed 96-well plates (#3904, BECTON-DICKINSON, Franklin Lakes, NJ) in Ham's F12 culture medium (MEDiatech, Herndon, VA) supplemented with 10% fetal bovine serum, 25 mM HEPES and 500 $\mu\text{g}/\text{mL}$ (active) G418. Prior to running the assay, the culture medium was emptied from the 96 well plates. Fluo-3 calcium sensitive dye (Molecular Probes, Eugene, OR) was added to each well (dye solution: 1 mg FLUO-3 AM, 440 μL DMSO and 440 μL 20% pluronic acid in DMSO, diluted 1:4, 50 μL diluted solution per well). Plates were covered with aluminum foil and incubated at 37°C for 1-2 hours. After the incubation, the dye was emptied from the plates, cells were washed once in 100 μL KRH buffer (0.05 mM KCl, 0.115 M NaCl, 9.6 mM NaH_2PO_4 , 0.01 mM MgSO_4 , 25 mM HEPES, pH 7.4) to remove excess dye; after washing, 80 μL KRH buffer was added to each well.

Fluorescence response was monitored upon the addition of either human MCH receptor or test compound by a FLIPRTM plate reader (Molecular Devices, Sunnyvale, CA) by excitation at 480 nm and emission at 530 nm.

In order to measure the ability of a test compound to antagonize the response of cells expressing MCH receptors to MCH, the EC_{50} of MCH was first determined. An additional 20 μL of KRH buffer and 1 μL DMSO was added to each well of cells, prepared as described above. 100 μL human MCH in KRH buffer was automatically transferred by the FLIPR instrument to each well. An 8-point concentration response curve, with final MCH concentrations of 1 nM to 3 μM , was used to determine MCH EC_{50} .

35 Test compounds were dissolved in DMSO, diluted in 20 μL KRH buffer, and added to cells prepared as described above. The 96 well plates containing prepared cells and test compounds were incubated in the dark, at room temperature for 0.5–6 hours. It is important that

the incubation not continue beyond 6 hours. Just prior to determining the fluorescence response, 100 μ l human MCH diluted in KRH buffer to $2 \times EC_{50}$ was automatically added by the FLIPR instrument to each well of the 96 well plate for a final sample volume of 200 μ l and a final MCH concentration of EC_{50} . The final concentration of test compounds in the assay wells was between 1 μ M and 5 μ M. Typically, cells exposed to one EC_{50} of MCH exhibit a fluorescence response of about 10,000 Relative Fluorescence Units. Antagonists of the MCH receptor exhibit a response that is significantly less than that of the control cells to the $p \leq 0.05$ level, as measured using a parametric test of statistical significance. Typically, antagonists of the MCH receptor decreased the fluorescence response by about 20%, preferably by about 50%, and most preferably by at least 80% as compared to matched controls.

The ability of a compound to act as an agonist of the MCH receptor was determined by measuring the fluorescence response of cells expressing MCH receptors, using the methods described above, in the absence of MCH. Compounds that cause cells to exhibit fluorescence above background are MCH receptor agonists.

Example 4

Determination of Dopamine D_2 and D_4 Receptor Binding Activity

This Example illustrates a representative standard assay for determining the binding affinity of compounds to dopamine D_4 and D_2 receptors.

Pellets of Chinese hamster ovary (CHO) cells containing recombinantly expressing primate D_2 , human D_4 dopamine receptors were used for the assays. The sample was homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer containing 120 mM NaCl, 5 mM $MgCl_2$ and 1 mM EDTA at 4°C and pH 7.4. The sample was then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample was then centrifuged as described and the final tissue sample was frozen until use. The tissue was resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 120 mM NaCl.

Incubations for dopaminergic binding are carried out at 25°C and contain 0.4 ml of tissue sample, 0.1 nM 3H -YM 09151-2 (Nemonapride, cis-5-Chloro-2-methoxy-4-(methylamino)-N-(2-methyl-2-(phenylmethyl)-3-pyrrolidinyl)benzamide) and the compound of interest in a total incubation of 1.0 ml. Nonspecific binding was defined as that binding found in the presence of 1 micromolar spiperone; without further additions, nonspecific binding was less than 20% of total binding.

Example 5

MDCK Cytotoxicity Assay

This Example illustrates the evaluation of compound toxicity using a Madin Darby canine kidney (MDCK) cell cytotoxicity assay.

1 μL of test compound is added to each well of a clear bottom 96-well plate (PACKARD, Meriden, CT) to give final concentration of compound in the assay of 10 micromolar, 100 micromolar or 200 micromolar. Solvent without test compound is added to control wells.

5 MDCK cells, ATCC no. CCL-34 (American Type Culture Collection, Manassas, VA), are maintained in sterile conditions following the instructions in the ATCC production information sheet. Confluent MDCK cells are trypsinized, harvested, and diluted to a concentration of 0.1×10^6 cells/ml with warm (37°C) medium (VITACELL Minimum Essential Medium Eagle, ATCC catalog # 30-2003). 100 μL of diluted cells is added to each well, except
10 for five standard curve control wells that contain 100 μL of warm medium without cells. The plate is then incubated at 37°C under 95% O_2 , 5% CO_2 for 2 hours with constant shaking. After incubation, 50 μL of mammalian cell lysis solution is added per well, the wells are covered with PACKARD TOPSEAL stickers, and plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes.

15 Compounds causing toxicity will decrease ATP production, relative to untreated cells. The PACKARD, (Meriden, CT) ATP-LITE-M Luminescent ATP detection kit, product no. 6016941, is generally used according to the manufacturer's instructions to measure ATP production in treated and untreated MDCK cells. PACKARD ATP LITE-M reagents are allowed to equilibrate to room temperature. Once equilibrated, the lyophilized substrate solution
20 is reconstituted in 5.5 mL of substrate buffer solution (from kit). Lyophilized ATP standard solution is reconstituted in deionized water to give a 10 mM stock. For the five control wells, 10 μL of serially diluted PACKARD standard is added to each of the standard curve control wells to yield a final concentration in each subsequent well of 200 nM, 100 nM, 50 nM, 25 nM and 12.5 nM. PACKARD substrate solution (50 μL) is added to all wells, which are then covered, and the
25 plates are shaken at approximately 700 rpm on a suitable shaker for 2 minutes. A white PACKARD sticker is attached to the bottom of each plate and samples are dark adapted by wrapping plates in foil and placing in the dark for 10 minutes. Luminescence is then measured at 22°C using a luminescence counter (*e.g.*, PACKARD TOPCOUNT Microplate Scintillation and Luminescence Counter or TECAN SPECTRAFLUOR PLUS), and ATP levels calculated from
30 the standard curve. ATP levels in cells treated with test compound(s) are compared to the levels determined for untreated cells. Cells treated with 10 μM of a preferred test compound exhibit ATP levels that are at least 80%, preferably at least 90%, of the untreated cells. When a 100 μM concentration of the test compound is used, cells treated with preferred test compounds exhibit ATP levels that are at least 50%, preferably at least 80%, of the ATP levels detected in untreated
35 cells.

Example 6Microsomal *in vitro* half-life

This Example illustrates the evaluation of compound half-life values ($t_{1/2}$ values) using a representative liver microsomal half-life assay.

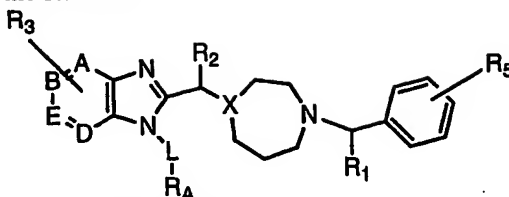
5 Pooled human liver microsomes are obtained from XenoTech LLC, 3800 Cambridge St., Kansas City, Kansas 66103 (catalog # H0610). Such liver microsomes may also be obtained from In Vitro Technologies (Baltimore, MD) or Tissue Transformation Technologies (Edison, NJ). Six test reactions are prepared, each containing 25 μ l microsomes, 5 μ l of a 100 μ M solution of test compound, and 399 μ l 0.1 M phosphate buffer (19 mL 0.1 M NaH_2PO_4 , 81 mL 10 0.1 M Na_2HPO_4 , adjusted to pH 7.4 with H_3PO_4). A seventh reaction is prepared as a positive control containing 25 μ l microsomes, 399 μ l 0.1 M phosphate buffer, and 5 μ l of a 100 μ M solution of a compound with known metabolic properties (e.g., DIAZEPAM or CLOZEPINE). Reactions are preincubated at 39°C for 10 minutes.

15 CoFactor Mixture is prepared by diluting 16.2 mg NADP and 45.4 mg Glucose-6-phosphate in 4 mL 100 mM MgCl_2 . Glucose-6-phosphate dehydrogenase solution is prepared by diluting 214.3 μ l glucose-6-phosphate dehydrogenase suspension (Boehringer-Mannheim catalog no. 0737224, distributed by Roche Molecular Biochemicals, Indianapolis, IN) into 1285.7 μ l distilled water. 71 μ l Starting Reaction Mixture (3 mL CoFactor Mixture; 1.2 mL Glucose-6-phosphate dehydrogenase solution) is added to 5 of the 6 test reactions and to the positive 20 control. 71 μ l 100 mM MgCl_2 is added to the sixth test reaction, which is used as a negative control. At each time point (0, 1, 3, 5, and 10 minutes), 75 μ l of each reaction mix is pipetted into a well of a 96-well deep-well plate containing 75 μ l ice-cold acetonitrile. Samples are vortexed and centrifuged 10 minutes at 3500 rpm (Sorval T 6000D centrifuge, H1000B rotor). 75 μ l of supernatant from each reaction is transferred to a well of a 96-well plate containing 150 25 μ l of a 0.5 μ M solution of a compound with a known LCMS profile (internal standard) per well. LCMS analysis of each sample is carried out and the amount of unmetabolized test compound is measured as AUC, compound concentration vs. time is plotted, and the $t_{1/2}$ value of the test compound is extrapolated.

30 Preferred compounds of the present invention exhibit *in vitro* $t_{1/2}$ values of greater than 10 minutes and less than 4 hours, preferably between 30 minutes and 1 hour, in human liver microsomes.

What is claimed is:

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A, B, E, D and X each independently represent CH or N, with the proviso that not more than two of A, B, E and D represent N;

R₁ is:

- (i) hydrogen, -C(=O)-NH₂, -SO₂NH₂, or -COOH; or
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is optionally substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₂ is:

- (i) hydrogen, halogen, hydroxy, -C(=O)-NH₂, -SO₂NH₂, or -COOH; or
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₃ represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D, and each of which is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂, and -COOH; and
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, and mono- and di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

L is C₁-C₆alkyl;

R_A is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl,

haloC₁-C₈alkyl, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di(C₁-C₈alkyl)amino, C₁-C₈carbamate and 5- to 10-member carbocyclic and heterocyclic groups; and

R₃ represents from 0 to 3 substituents of phenyl, each of which is independently selected from:

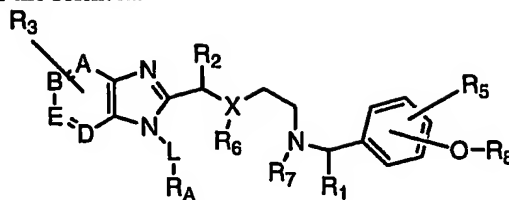
- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)NH₂, -SO₂NH₂ and -COOH; and
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, mono- and di-(C₁-C₈alkyl)carboxamido, and fused and pendant 3- to 10-member carbocyclic and heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl.

2. A compound according to claim 1, wherein (i) L is -CH₂- and (ii) R_A is phenyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from halogen, C₁-C₈alkyl, haloC₁-C₈alkyl, C₁-C₈alkoxy and haloC₁-C₈alkoxy.
3. A compound according to claim 1, wherein R₁ and R₂ are independently hydrogen or C₁-C₈alkyl.
4. A compound according to claim 1, wherein at least one R₅ is dioxolane.
5. A compound according to claim 1, wherein at least one R₅ is a halogen.
6. A compound according to claim 5, wherein at least one R₅ is C₁-C₄alkoxy.
7. A compound according to claim 1, wherein A, B, E and D are CH.
8. A compound according to claim 1, wherein A, E and D are CH and B is N.
9. A compound according to claim 1, wherein X is N.
10. A compound according to claim 1, wherein the compound exhibits a K_i of 100 nanomolar or less in an MCH receptor ligand binding assay.
11. A compound according to claim 1, wherein the compound exhibits a K_i of 10 nanomolar or less in an MCH receptor ligand binding assay.
12. A pharmaceutical composition comprising a compound according to claim 1 in combination with a physiologically acceptable carrier or excipient.
13. A compound according to claim 1, wherein the compound is selected from:

- 1-(2,4-dichloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(2,5-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,4-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,4-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,5-bis-trifluoromethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,5-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-benzyloxy-benzyl)-2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-bromo-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-chloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-*tert*-butyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-biphenyl-4-ylmethyl-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-biphenyl-4-ylmethyl-2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 2-(4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl)-1-naphthalen-2-ylmethyl-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-methoxy-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2,4-dichloro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2,4-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2,5-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-bromo-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-chloro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-fluoro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-fluoro-5-methoxy-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-methyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(3,4-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(3,5-dimethoxy-benzyl)-1H-benzoimidazole;

- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-dimethyl-benzyl)-1*H*-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-bis-trifluoromethyl-benzyl)-1*H*-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-bromo-benzyl)-1*H*-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-[1-(2-fluoro-phenyl)-ethyl]-1*H*-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-benzyl-1*H*-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-*tert*-Butyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1*H*-benzoimidazole;
- 2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-chloro-benzyl)-1*H*-benzoimidazole;
- 2-[4-(2-Fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-trifluoromethyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-[1-(2-fluoro-phenyl)-ethyl]-1*H*-benzoimidazole;
- 2-[4-(2-Fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-1-ylmethyl-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2,5-dimethyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,4-difluoro-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,4-dimethyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3,5-dimethyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4-bromo-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4-*tert*-butyl-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(3-chloro-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(4-fluoro-benzyl)-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-benzyl-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-2-ylmethyl-1*H*-benzoimidazole;
- 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-1-ylmethyl-1*H*-benzoimidazole;
- 2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-benzyl-1*H*-benzoimidazole;
- and
- 2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-(3,5-dimethoxy-benzyl)-1*H*-benzoimidazole.

14. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A, B, E, D and X each independently represent CH or N, with the proviso that not more than two of A,

B, E and D represent N;

R₁ is:

- (i) hydrogen, -C(=O)-NH₂, -SO₂NH₂, or -COOH; or
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₂ is:

- (i) hydrogen, halogen, hydroxy, -C(=O)-NH₂, -SO₂NH₂, or -COOH; or
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₃ represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D, and each of which is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ and -COOH; and
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, and mono- and di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

L is C₁-C₆alkyl;

R_A is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl, haloC₁-C₈alkyl, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₁-C₈alkanoyl, C₁-C₈alkanoyloxy, C₁-

C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate and 5- to 10-membered carbocyclic and heterocyclic groups;

R₅ represents from 0 to 3 substituents, each of which is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂, and -COOH;
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, mono- and di-(C₁-C₈alkyl)carboxamido, and fused and pendant 3- to 10-membered carbocyclic and heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; and
- (iii) substituents that are joined to R₆ to form a 5- or 6-membered heterocyclic ring;

R₆ and R₇ are independently:

- (i) hydrogen, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂, or -COOH;
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; or
- (iii) joined to form, with XCH₂CH₂N, a 5- to 7-member heterocyclic ring, wherein the ring is unsubstituted or substituted with from 1 to 3 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; and

R₈ is hydrogen, C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₂-C₈alkanoyl, C₂-C₈alkyl ether, haloC₁-C₈alkyl, haloC₁-C₈alkoxy or a substituent that is joined to R₅ to form a 5- or 6-member heterocyclic ring.

15. A compound according to claim 14, wherein (i) L is -CH₂- and (ii) R_A is phenyl, unsubstituted or substituted with from 1 to 3 substituents independently selected from halogen, C₁-C₈alkyl, haloC₁-C₈alkyl, C₁-C₈alkoxy and haloC₁-C₈alkoxy.

16. A compound according to claim 15, wherein R₆ and R₇ jointly with XCH₂CH₂N form a 6- or 7-membered heterocyclic ring.

17. A compound according to claim 15, wherein R₁ and R₂ are independently hydrogen or C₁-C₈alkyl.

18. A compound according to claim 17, wherein R₈ and R₅ are joined to form dioxolane.

19. A compound according to claim 14, wherein X is N.

20. A compound according to claim 19, wherein (i) L is $-CH_2-$ and (ii) R_A is phenyl, unsubstituted or substituted with a halogen, C_1-C_8 alkyl, halo C_1-C_8 alkyl, C_1-C_8 alkoxy or halo C_1-C_8 alkoxy.

21. A compound according to claim 14, wherein the compound exhibits a K_i of 100 nanomolar or less in an MCH receptor ligand binding assay.

22. A compound according to claim 14, wherein the compound exhibits a K_i of 10 nanomolar or less in an MCH receptor ligand binding assay.

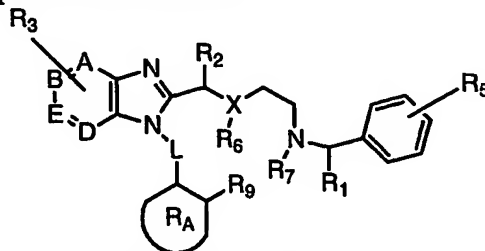
23. A pharmaceutical composition comprising a compound according to claim 14 in combination with a physiologically acceptable carrier or excipient.

24. A compound according to claim 14, wherein the compound is selected from:

- 1-(2,4-dichloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(2,5-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(2-fluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1H-benzoimidazole;
- 1-(2-fluoro-benzyl)-2-[4-(3-methoxy-benzyl)-piperazin-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,4-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,4-dimethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,5-bis-trifluoromethyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(3,5-difluoro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-bromo-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-chloro-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-(4-*tert*-butyl-benzyl)-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-benzyl-2-[4-(3-methoxy-benzyl)-piperazin-1-ylmethyl]-1H-benzoimidazole;
- 1-biphenyl-4-ylmethyl-2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 1-Biphenyl-4-ylmethyl-2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1H-benzoimidazole;
- 1-biphenyl-4-ylmethyl-2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1H-benzoimidazole;
- 2-[4-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-naphthalen-2-ylmethyl-1H-benzoimidazole;
- 2-[4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;

- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2,4-dichloro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2,4-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2,5-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-bromo-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-chloro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-fluoro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-fluoro-5-methoxy-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(2-methyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,4-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-dimethoxy-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(3,5-bis-trifluoromethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-bromo-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-[1-(2-fluoro-phenyl)-ethyl]-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-benzyl-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-[1,4]diazepan-1-ylmethyl)-1-(4-*tert*-Butyl-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,4-difluoro-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,5-difluoro-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2,6-difluoro-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-fluoro-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-5-trifluoromethyl-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-imidazo[4,5-c]pyridine;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(3,5-dimethoxy-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(3,5-dimethyl-benzyl)-1H-benzoimidazole;
- 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(4-piperidin-1-ylmethyl-benzyl)-1H-benzoimidazole;
- 2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-[1-phenyl-ethyl]-1H-benzoimidazole;

25. A compound of the formula:



(i) hydrogen, $-\text{C}(=\text{O})-\text{NH}_2$, $-\text{SO}_2\text{NH}_2$, or $-\text{COOH}$; or

- (ii) (C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

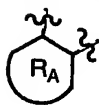
R₂ is:

- (i) hydrogen, halogen, hydroxy, -C(=O)-NH₂, -SO₂NH₂, or -COOH; or
 (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₃ represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D, and each substituent is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ and -COOH; and
 (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, and mono- and di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

L is C₁-C₆alkyl;



is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl, haloC₁-C₈alkyl, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate and 5- to 10-membered carbocyclic and heterocyclic groups;

R₅ represents from 0 to 3 substituents, each of which is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂, or -COOH; and
 (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, mono- and di-(C₁-C₈alkyl)carboxamido, and fused and pendant 3- to 10-membered carbocyclic and

heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₆ and R₇ are independently:

- (i) hydrogen, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ or -COOH;
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; or
- (iii) joined to form, with XCH₂CH₂N, a 5- to 7-membered heterocyclic ring, wherein the ring is unsubstituted or substituted with from 1 to 3 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; and

R₉ is hydroxy, C₁-C₈alkoxy, haloC₁-C₈alkoxy, C₂-C₈alkanoyloxy or haloC₂-C₈alkanoyloxy.

26. A compound according to claim 25, wherein L is -CH₂- or -CH(CH₃)-, and R_A is unsubstituted or substituted phenyl.

27. A compound according to claim 26, wherein R₉ is hydroxy, C₁-C₆alkoxy or haloC₁-C₆alkoxy.

28. A compound according to claim 26, wherein two R₅ substituents join to form dioxolane.

29. A compound according to claim 25, wherein R₆ and R₇ jointly with XCH₂CH₂N form a 6- or 7-membered heterocyclic ring.

30. A compound according to claim 25, wherein X is N.

31. A compound according to claim 25, wherein R₁ and R₂ are independently hydrogen or C₁-C₆alkyl.

32. A compound according to claim 25, wherein the compound exhibits a K_i of 100 nanomolar or less in an MCH receptor ligand binding assay.

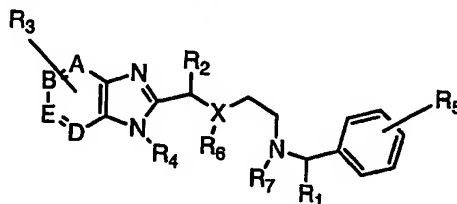
33. A compound according to claim 25, wherein the compound exhibits a K_i of 10 nanomolar or less in an MCH receptor ligand binding assay.

34. A pharmaceutical composition, comprising a compound according to claim 25 in combination with a physiologically acceptable carrier or excipient.

35. A compound according to claim 25, wherein the compound is selected from:
- 1-(2-methoxy-benzyl)-2-(4-naphthalen-1-ylmethyl-piperazin-1-ylmethyl)-1H-benzoimidazole;
 - 2-(4-benzo[1,3]dioxol-5-ylmethyl)-[1,4]diazepan-1-ylmethyl-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-5-trifluoromethyl-1H-benzoimidazole;
 - 2-(4-Benzo[1,3]dioxol-5-ylmethyl-piperazin-1-ylmethyl)-1-(2-methoxy-benzyl)-1H-imidazo[4,5-c]pyridine;
 - 2-[1-(2-fluoro-5-methoxybenzyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[1-(4-benzo[1,3]dioxol-5-ylmethyl-piperazin-1-yl)-ethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[1-(4-fluoro-3-methoxybenzyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[1-(6-chloro-benzo[1,3]dioxol-5-ylmethyl)-piperidin-4-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(1-Benzo[1,3]dioxol-5-yl-ethyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(2-fluoro-3-methoxy-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(2-fluoro-5-methoxy-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(2-fluoro-5-methoxy-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(3,4-difluoro-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(3,4-dimethyl-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(4-chloro-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(4-methyl-benzyl)-piperazin-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - 2-[4-(5-bromo-2-fluoro-benzyl)-[1,4]diazepan-1-ylmethyl]-1-(2-methoxy-benzyl)-1H-benzoimidazole;
 - and
 - 9-Ethyl-3-(4-[1-(2-methoxy-benzyl)-1H-benzoimidazol-2-ylmethyl]-piperazin-1-ylmethyl)-9H-carbazole.

36. A pharmaceutical composition according to any one of claims 12, 23 or 34, wherein the composition is formulated as an injectible fluid, an aerosol, a cream, a gel, a pill, a capsule, a syrup or a transdermal patch.

37. A method for treating a disease or disorder associated with pathogenic melanin concentrating hormone receptor activation, comprising administering to a patient in need of such treatment an effective amount of a compound having the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A, B, E, D and X each independently represent CH or N, with the proviso that not more than two of A, B, E and D represent N;

R₁ is:

- (i) hydrogen, -C(=O)-NH₂, -SO₂NH₂ or -COOH; or
- (ii) (C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido, or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₂ is:

- (i) hydrogen, halogen, hydroxy, -C(=O)-NH₂, -SO₂NH₂ or -COOH; or
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkyl ether, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- or di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- or di-(C₁-C₈alkyl)sulfonamido or mono- or di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₃ represents 0 to 4 substituents, each of which is linked to a carbon atom at A, B, E or D, and each substituent is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, -C(=O)-NH₂, -SO₂NH₂ and -COOH; and
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, and mono- and di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl;

R₄ is:

- (i) hydrogen, -C(=O)-NH₂, -SO₂NH₂ or -COOH;
- (ii) C₁-C₈alkyl, C₂-C₈alkenyl, C₂-C₈alkynyl, C₁-C₈alkoxy, C₂-C₈alkanoyl, C₂-C₈alkanoyloxy, C₁-C₈alkoxycarbonyl, C₁-C₈carbonate, C₁-C₈alkylthio, mono- and di-(C₁-C₈alkyl)amino, C₁-C₈carbamate, mono- and di-(C₁-C₈alkyl)sulfonamido, and mono- and di-(C₁-C₈alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C₁-C₈alkyl and haloC₁-C₈alkyl; or

- (iii) $L-R_A$, wherein L is C_1-C_8 alkyl; and R_A is a 5- to 7-membered carbocyclic or heterocyclic ring, unsubstituted or substituted with from 1 to 4 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl, halo C_1-C_8 alkyl, C_1-C_8 alkoxy, halo C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- and di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate and 5- to 10-membered carbocyclic and heterocyclic groups;

R_5 represents from 0 to 3 substituents, each of which is independently selected from:

- (i) halogen, hydroxy, amino, cyano, nitro, $-C(=O)-NH_2$, $-SO_2NH_2$ and $-COOH$;
- (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- and di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- and di- $(C_1-C_8$ alkyl)sulfonamido, mono- and di- $(C_1-C_8$ alkyl)carboxamido, and fused and pendant 3- to 10-membered carbocyclic and heterocyclic groups, each of which is unsubstituted or substituted with from 1 to 9 secondary substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl; and
- (iii) substituents that join with a second substituent to form a 5- to 7-membered carbocyclic or heterocyclic ring; and

R_6 and R_7 are independently:

- (i) hydrogen, amino, cyano, nitro, $-C(=O)-NH_2$, $-SO_2NH_2$ or $-COOH$;
- (ii) C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_1-C_8 alkoxy, C_2-C_8 alkanoyl, C_2-C_8 alkyl ether, C_2-C_8 alkanoyloxy, C_1-C_8 alkoxycarbonyl, C_1-C_8 carbonate, C_1-C_8 alkylthio, mono- or di- $(C_1-C_8$ alkyl)amino, C_1-C_8 carbamate, mono- or di- $(C_1-C_8$ alkyl)sulfonamido, or mono- or di- $(C_1-C_8$ alkyl)carboxamido, each of which is unsubstituted or substituted with from 1 to 9 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl; or
- (iii) joined to form, with XCH_2CH_2N , a 5- to 7-member heterocyclic ring, wherein the ring is unsubstituted or substituted with from 1 to 3 substituents independently selected from hydroxy, halogen, amino, cyano, nitro, C_1-C_8 alkyl and halo C_1-C_8 alkyl.

38. A method according to claim 37 wherein the disease or disorder is an eating disorder, sexual disorder, obesity, diabetes, heart disease or stroke.

39. A method according to claim 37, wherein the compound or modulator is administered orally.

40. A method according to claim 37, wherein the compound or modulator is administered intranasally, intravenously or topically.

41. A method according to claim 37, wherein the patient is a human or a dog.

42. A method according to claim 37, wherein the compound is a compound according to claim 1.
43. A method according to claim 35, wherein the compound is a compound according to claim 14 or claim 25.
44. A compound according to any one of claims 1, 14 or 25, wherein the compound is radiolabeled.
45. A method for determining the presence or absence of melanin concentrating hormone receptor in a sample, comprising the steps of:
- (a) contacting a sample with radiolabeled compound according to claim 44 under conditions that permit binding of the agent to melanin concentrating hormone receptor; and
 - (b) detecting a level of agent bound to melanin concentrating hormone receptor, and therefrom determining the presence or absence of melanin concentrating hormone receptor in the sample.
46. A method according to claim 45, wherein step of detection comprises:
- (i) separating unbound agent from bound agent; and
 - (ii) detecting the presence or absence of bound agent in the sample.
47. A method for modulating binding of melanin concentrating hormone to a melanin concentrating hormone receptor *in vitro*, the method comprising contacting melanin concentrating hormone receptor with a compound according to any one of claims 1, 14 or 25 under conditions and in an amount sufficient to detectably modulate melanin concentrating hormone binding to melanin concentrating hormone receptor.
48. A method for modulating binding of melanin concentrating hormone to melanin concentrating hormone receptor, the method comprising contacting cells expressing melanin concentrating hormone receptor with a compound according to any one of claims 1, 14 or 25 in an amount sufficient to detectably modulate melanin concentrating hormone binding to cells expressing a cloned melanin concentrating hormone receptor *in vitro*.
49. A method for modulating binding of melanin concentrating hormone to melanin concentrating hormone receptor in a patient, comprising administering to a patient a compound according to any one of claims 1, 14 or 25, and thereby modulating binding of melanin concentrating hormone to melanin concentrating hormone receptor in the patient.
50. A method according to any one of claims 47-49, wherein the modulation is inhibition.

51. A method according to any one of claims 47-49, wherein the melanin concentrating hormone receptor is a human melanin concentrating hormone receptor.
52. A packaged pharmaceutical preparation, comprising:
- (a) a pharmaceutical composition according to any one of claims 12, 23 or 34 in a container; and
 - (b) instructions for using the composition to treat a patient suffering from a disorder responsive to melanin concentrating hormone receptor antagonism or agonism.
53. A packaged pharmaceutical preparation according to claim 52, wherein the patient is suffering from an eating disorder, sexual disorder, obesity, diabetes, heart disease or stroke.
54. Use of a compound according to any one of claims 1, 14 or 25 for the manufacture of a medicament for treating a disease or disorder associated with pathogenic melanin concentrating hormone receptor activation.

SEQUENCE LISTING

<110> DeSimone, Robert W.
Peterson, John
Steenstra, Cheryl
Shen, Yiping
Gustavson, Linda
Mach, Christopher
Hutchison, Alan

<120> MELANIN CONCENTRATING HORMONE RECEPTOR LIGANDS: SUBSTITUTED 2-(4-BENZYL-PIPERAZIN-1-YLMETHYL)- AND 2-(4-BENZYL-DIAZEPAN-1-YLMETHYL)-1H-BENZOIMIDAZOLE ANALOGUES

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